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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On 3/14/05

TOWNSEND and TOWNSEND and CREW LLP

By: _____

PATENT
Attorney Docket No.: 021706-000420US
Client Ref. No.: 2024 TTC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Albert Zorko Abram, et al.

Application No.: 10/763,379

Filed: January 23, 2004

For: PHARMACEUTICAL FOAM

Customer No.: 20350

Confirmation No. 7565

Examiner: HAGIHIGHATIAN, MINA

Technology Center/Art Unit: 1616

PETITION TO MAKE SPECIAL UNDER 37 C.F.R. § 1.102(d)

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby respectfully petition to make special the above-referenced patent application, as an invention according to M.P.E.P. § 708.02(VIII), so that examination of the application may be advanced. Please charge $130.00, pursuant to 37 C.F.R. § 1.17(h), to Deposit Account 20-1430. Please charge any additional fees or credit overpayment to the above Deposit Account. This petition is submitted in triplicate.

03/18/2005 ZJUHAR1 00000023 201430 10763379
01 FC:1464 130.00 DA

REMARKS

Upon entry of the preliminary amendment submitted with this petition, claims 1-8, 10-12, 14-62 and 64 are pending in this application and presented for examination. Petitioners respectfully petition for early examination on the merits.

Applicants hereby respectfully petition to make special the above-referenced patent application, as an invention according to M.P.E.P. § 708.02 (VIII). Under M.P.E.P. § 708.02 (VIII), a new application may be granted special status provided Applicants comply with each of the following items:

(A) Submit a petition to make special accompanied by the fee set forth in 37 CFR 1.17(h);

(B) Present all claims directed to a single invention, or if the Office determines that all the claims presented are not obviously directed to a single invention, will make an election without traverse as a prerequisite to the grant of special status;

(C) Submit a statement(s) that a pre-examination search was made, listing the field of search by class and subclass, publication, Chemical Abstracts, foreign patents, etc. A search made by a foreign patent office satisfies this requirement if the claims in the corresponding foreign application are of the same or similar scope to the claims in the U.S. application for which special status is requested;

(D) Submit one copy of each of the references deemed most closely related to the subject matter encompassed by the claims if said references are not already of record; and

(E) Submit a detailed discussion of the references, which discussion points out, with the particularity required by 37 CFR 1.111 (b) and (c), how the claimed subject matter is patentable over the references.

With respect to item (A), Applicants respectfully submit herewith a petition to make special accompanied by the fee set forth in 37 CFR 1.17(h).

With respect to item (B), Applicants present herewith claims 1-8, 10-12, 14-62 and 64 directed to a single invention. Applicants believe all claims pending are directed to a single invention. However, if the U.S.P.T.O. determines that the claims presented are not directed to a single invention, Applicants acknowledge that an election without traverse will be made though the established telephone restriction practice.

With respect to item (C), Applicants submit that a pre-examination search was made at the Australian Patent Office for the corresponding international application PCT/AU2004/000088. A copy of the search report is of record and a copy is enclosed herewith. The PCT Search Report lists the field of search by class and subclass (Internationally). Moreover, according to the Search Report, the DWPI and CAplus electronic databases were also searched. Applicants make no admissions regarding the materiality of any of the references cited herein, or whether any of the references are prior art with respect to the present invention.

With respect to item (D), the submission of one copy each of the references deemed most closely related to the subject matter encompassed by the claims have previously been made of record, submitted in an International Search Report mailed on April 26, 2004. Copies are also enclosed herewith.

With respect to item (E), Applicants submit herewith a detailed discussion of the references, which discussion points out, with the particularity required by 37 CFR 1.111 (b) and (c), how the claimed subject matter is novel and unobvious over the references.

THE PRESENT INVENTION

The present invention relates to a topical delivery composition that is a quick-breaking temperature sensitive foam, use of a quick-breaking temperature sensitive foam in the percutaneous treatment of acne, methods for modulating a foam characteristic of a quick-breaking temperature sensitive foam, and a topical delivery composition.

The present invention claims priority to U.S. Provisional Application Nos. 60/442,280, filed January 24, 2003 and 60/454,832, filed March 13, 2003.

Claims 1, 39, 53 and 64 are independent.

Claim 1 sets forth a topical delivery composition that is a quick-breaking temperature sensitive foam, that has a quick-breaking foaming agent comprised of a C_1-C_6 alcohol, a C_{14}-C_{22} alcohol, water and a surfactant.

Claim 39 sets forth a method for the percutaneous treatment of acne by applying a quick-breaking temperature sensitive foam comprising clindamycin.

Claim 53 sets forth a method for modulating a quick-breaking temperature sensitive foam by changing the C_1-C_6 alcohol to water ratio in the quick-breaking alcoholic foaming agent.

Claim 64 sets forth a topical composition in a pressurized container comprising up to 15% w/w of a topical combination of clindamycin phosphate and benzoyl peroxide, wherein the composition is a foam after release from the container.

DETAILED DISCUSSION OF THE REFERENCES

References:

1. **U.S. Publication No. 2003/0113385**
2. **PCT Publication No. WO 03/039559**
3. **French Patent Application No. 2 677 369 A1**

1. U.S. Publication No. 2003/0113385 ("the '385 publication")

The '385 publication discloses pressurized foam compositions (paragraphs 0021-0030 and 0063-0064) containing tea tree oil. The '385 publication does not teach or suggest a quick-breaking temperature sensitive foam, or any kind of foam comprising a quick-breaking foaming agent comprising a C_1-C_6 alcohol, a C_{14}-C_{22} alcohol, water and a surfactant, as set forth in independent claim 1.

The '385 publication discloses using mixed tea tree oil and antibiotic compositions in veterinary medicine, particularly in treating mastitis and metritis in agricultural

animals and small animals. The '385 publication does not teach or suggest methods for the percutaneous treatment of acne, as set forth in independent claim 39. The '385 publication does not teach or suggest using any kind of foam, much less a composition comprising clindamycin phosphate and benzoyl peroxide as set forth in independent claim 64.

The '385 publication does not teach or suggest a method for modulating a foam characteristic of a quick-breaking temperature sensitive foam by changing the C_1-C_6 alcohol to water ratio in the quick-breaking alcoholic foaming agent, as set forth in independent claim 53. The '385 publication does not teach or suggest an alcoholic foaming agent.

2. PCT Publication No. WO 03/039559 ("the '559 publication")

The '559 publication discloses non-aqueous pharmaceutical foams comprising a fungicide, a bacteriostatic sulphonamide and an antibacterial compound. The '559 publication discloses that the foams collapse and form a protective layer. The '559 publication does not teach or suggest a quick-breaking temperature sensitive foam, or any kind of foam comprising a quick-breaking foaming agent comprising a C_1-C_6 alcohol, a C_{14}-C_{22} alcohol, water and a surfactant, as set forth in independent claim 1. The foam formulations disclosed in the '559 publication (Example II.14 on page 41 of the '559 publication) are derived from a non-aqueous ointment (*Id.*, Example II.1 on page 34), and do not contain water or a surfactant, or a C_1-C_6 alcohol as a listed ingredient.

The primary purpose of the foam formulations of the '559 publication is to treat epithelial injuries, such as ulcers and burns (*see*, *Id.* at page 5, 2nd full paragraph). The '559 publication does not teach or suggest methods for the percutaneous treatment of acne, as set forth in independent claim 39. The '559 publication does not teach or suggest using any kind of foam, much less a composition comprising clindamycin phosphate and benzoyl peroxide as set forth in independent claim 64.

The '559 publication does not teach or suggest a method for modulating a foam characteristic of a quick-breaking temperature sensitive foam by changing the C_1-C_6 alcohol to water ratio in the quick-breaking alcoholic foaming agent, as set forth in independent claim 53. The '559 publication does not teach or suggest an alcoholic foaming agent.

3. French Patent Application No. 2 677 369 A1 ("the '369 application")

The '369 application discloses aerosol foams containing a self-emulsifying wax and propylene glycol that are useable as a carrier for medicinal actives. The '369 application does not teach or suggest a quick-breaking foam, but instead discloses that their foams are advantageously stable (*see*, page 2, lines 29-31 of the original publication and page 2, lines 16-18 of the English translation).

The '369 application does not teach or suggest a quick-breaking temperature sensitive foam, or any kind of foam comprising a quick-breaking foaming agent comprising a C_1-C_6 alcohol, a C_{14}-C_{22} alcohol, water and a surfactant, as set forth in independent claim 1. The '369 application does not disclose or suggest a quick-breaking foam comprising water and a C_{14}-C_{22} alcohol.

The '369 application does not teach or suggest methods for the percutaneous treatment of acne, as set forth in independent claim 39. The '369 application does not teach or suggest using any kind of foam, much less a composition comprising clindamycin phosphate and benzoyl peroxide as set forth in independent claim 64.

The '369 application discloses including general classes of medicinal actives that can be included in their foam formulations (*i.e.*, antibiotics, corticosteroids, anti-parasitic agents, anti-inflammatories, anti-infection agents and antiseptics) (*see*, page 2, lines 34-38 of the original publication and page 2, lines 21-23 of the English translation). The '369 application does not teach or suggest methods of treating any particular disease or condition, any particular medicinal active, or which particular medicinal actives can be used to treat a particular disease or condition.

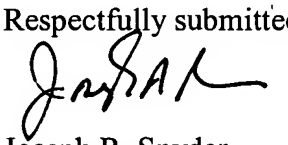
The '369 application does not teach or suggest a method for modulating a foam characteristic of a quick-breaking temperature sensitive foam by changing the C_1-C_6 alcohol to water ratio in the quick-breaking alcoholic foaming agent, as set forth in independent claim 53. The '385 publication does not teach or suggest an alcoholic foaming agent comprising alcohol and water.

CONCLUSION

In view of the foregoing remarks, Applicants believe all the requirements for petition to make special under 37 C.F.R § 1.102(d) and M.P.E.P. § 708.02 (VIII) have been met. Moreover, Applicants believe that the present invention is novel and unobvious over the art as set forth in the PCT Search Report. As such, Applicants respectfully request that the present petition be granted and examination on the merits of the subject application be conducted forthwith.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
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San Francisco, California 94111-3834
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JS:jlw

60426511 v1

PTO/SB/17 (12-04)

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 130

Complete if Known	
Application Number	10/763,379
Filing Date	January 23, 2004
First Named Inventor	Abram, Albert Zorko
Examiner Name	Mina Hagihighatian
Art Unit	1616
Attorney Docket No.	021706-000420US

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 20-1430 Deposit Account Name: Townsend and Townsend and Crew LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	-20 or HP = _____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____	-3 or HP = _____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____ / 50 =	_____ (round up to a whole number)	x _____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other: Petition to Make Special	$130

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 39,381	Telephone 925-472-5000
Name (Print/Type)	Joseph R. Snyder		Date March 14, 2005

60443611 v1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/000088

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 31/4025, A61K 7/40, A61 K 9/12, A61P 17/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
REFER TO ELECTRONIC DATABASE CONSULTED BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI and CAplus. Keywords: aerosol or spray, antibiotics or clindamycin, foam, water and surfactant, polysorbate or laureth or glycerol (w) monolaurate.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DERWENT Abstract Accession No.93-047146/06, Class A96 B07 D21, FR 2677369 A (SOC PROMOTION RECH & INNOVATION), 11 December 1991 Abstract	1, 2, 5, 6
P,X	US 2003/0113385 A (SCHLEICHER ET AL), 19 June 2003 Whole document	1, 2, 5, 6, 32
P,X	WO 2003/039559 A (HUMAN RT), 15 May 2003 Page 13, paragraph 4, page 18, line 30, page 20, paragraph 11, Example 14	1-6, 32

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report 1 MAR 2004
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **G.J. MCNEICE** Telephone No : (02) 6283 2055

International application No.
PCT/AU2004/000088

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
US	2003/0113385	WO	1999/038521	EP	1 054 681
WO	2003/039559	HU	0 104 790		END OF ANNEX

[19] FRENCH REPUBLIC

INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE [NATIONAL INDUSTRIAL PROPERTY INSTITUTE]

PARIS

[11] **Publication No.** ***2 677 369***
(for use only when ordering reproductions)

[21] **National registration No.** **91 06827**

[51] Int. Cl.[6]: **C 09K 3/30; A 61 K9/12, 7/00**

[12] **PATENT APPLICATION** **A1**

[22] **Filing Date:** 05.06.91

[30] **Priority:**

[43] **Publication date of application:** 11.12.92 Bulletin 92/50.

[56] **List of documents cited in search report:** *Refer to end of this application.*

[60] **References to other similar national documents:**

[71] **Applicant(s):** *SOCIETE DE PROMOTION, RECHERCHE ET INNOVATION TECHNOLOGIQUE (Not-for-profit organisation)* – FR.

[72] **Inventors:** Suck Catherine, Bret Pierre and Pozzi Jacques.

[73] **Holder(s):**

[74] **Agent:** Cabinet Pierre Loyer

[54] Aerosol foam

[57] Aerosol foam useable as a carrier for medicinal or cosmetic active principles.
It comprises an association of an emulsifier and a solvent, the emulsifier being a self-emulsifying wax and the solvent being propylene glycol.

[Bar code]

AEROSOL FOAM

The invention relates to an aerosol foam useable as a carrier for medicinal or cosmetic active principles.

For treating certain conditions, it is preferable to use topical products and to apply these products, an aerosol foam is a carrier which offers certain advantages by virtue of the availability of the molecules of active principles put in it, either in solution or in suspension.

The object of the invention is an aerosol foam useable as a carrier for medicinal or cosmetic active principles and which comprises an association of an emulsifier and a solvent, the emulsifier being a self-emulsifying wax and the solvent being propylene glycol.

According to other characteristics of the invention:

- in the case of a non-aqueous foam, it also comprises another emulsifier such as polyoxyethylene stearyl alcohol;
- in the case of an aqueous foam, it also comprises another emulsifier such as polysorbate 20, and water;
- it also comprises a glyceride of fatty acids and polyethylene glycol;
- it comprises preservatives such as methyl parahydroxybenzoate and propyl parahydroxybenzoate;
- in the case of non-aqueous foams, the constituents are in the following proportions:
  - emulsifiers: between 2.70 and 7.81%
  - solvent: between 92.19 and 97.30%
  - preservatives: about 0.14%
- in the case of aqueous foams, the constituents are in the following proportions:
  - emulsifiers: between 3.52 and 4.35%
  - solvent: between 42.00 and 64.16%
  - water: between 31.99 and 54.04%
  - preservatives: about 0.14%
- the foam propellant is taken from the group comprising hydrocarbons and fluorocarbons;
- the hydrocarbons are incorporated in a proportion of about 5.50%;
- the fluorocarbons are incorporated in a proportion of about 9.5%.

Examples of embodiments of aerosol foams according to the invention are given in the appended table. In this table, compositions A1 to A7 are aqueous compositions and compositions NA1 to NA7 are non-aqueous compositions.

In all the compositions:

- emulsifier 1 is a self-emulsifying wax,
- the solvent is propylene glycol,
- the preservative MPHB is methyl parahydroxybenzoate,
- the preservative PPHB is propyl parahydroxybenzoate,
- propellant 1 is butane.

In the aqueous compositions:

- emulsifier 2 is polysorbate 20,
- the glyceride is a glyceride of fatty acids and polyethylene glycol,
- propellant 2 is a freon.

In the non-aqueous compositions:

- emulsifier 2 is polyoxyethylene stearyl alcohol.

The foaming compositions according to the invention have several advantages, in particular:

- they are very stable;
- the constituents used are all accepted under pharmaceutical and cosmetic legislation;
- they can take up to 30% by weight of medicinal or cosmetic active principles such as, for example, liposomes, antibiotics, corticosteroids, anti-parasitic agents, anti-inflammatories, anti-infection agents or antiseptics;
- they are particularly well suited to the application of topical products.

TABLE

Aqueous	A1	A2	A3	A4	A5	A6	A7
Emulsifier 1	1.76	1.76	1.76	1.76	1.77	2.61	2.18
Emulsifier 2	1.76	1.76	1.76	1.76	1.77	1.74	1.74
Solvent	42.38	53.30	64.16	42.44	48.23	42.01	42.00
Glyceride	21.69					21.50	21.49
Water	32.27	43.18	32.32	54.04	48.23	31.99	31.99
MPHB	0.12	0.12	0.12	0.12	0.12	0.12	0.12
PPHB	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Propellant 1	5.50	5.50	5.50	5.50	5.50		
Propellant 2						9.47	9.51

Non-aqueous	NA1	NA2	NA3	NA4	NA5	NA6	NA7
Emulsifier 1	1.25	1.56	1.01	0.83	0.54	1.25	1.04
Emulsifier 2	4.99	6.25	4.04	3.32	2.16	5.00	4.17
Solvent	93.62	92.19	94.18	95.71	97.30	93.75	95.00
MPHB	0.12	0.12	0.12	0.12	0.12	0.12	0.12
PPHB	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Propellant 1	5.50	5.50	5.50	5.50	5.50	5.50	5.50

CLAIMS

1. An aerosol foam useable as a carrier for medicinal or cosmetic active principles, comprising an association of an emulsifier and a solvent, the emulsifier being a self-emulsifying wax, and the solvent being propylene glycol.

2. An aerosol foam according to claim 1 which, in the case of a non-aqueous foam, also comprises another emulsifier such as polyoxyethylene stearyl alcohol.

3. An aerosol foam according to claim 1 which, in the case of an aqueous foam, also comprises another emulsifier such as polysorbate 20, and water.

4. An aerosol foam according to claim 3 which also comprises a glyceride of fatty acids and polyethylene glycol.

5. An aerosol foam according to claim 1 which comprises preservatives such as methyl parahydroxybenzoate and propyl parahydroxybenzoate.

6. An aerosol foam according to both of claims 2 and 5 wherein, in the case of non-aqueous foams, the proportions of the constituents are as follows:

- emulsifiers: between 2.70 and 7.81%
- solvent: between 92.19 and 97.30%
- preservatives: about 0.14%

7. An aerosol foam according to both of claims 4 and 5 wherein, in the case of aqueous foams, the proportions of the constituents are as follows:

- emulsifiers: between 3.52 and 4.35%
- solvent: between 42.00 and 64.16%
- water: between 31.99 and 54.04%
- preservatives: about 0.14%

8. An aerosol foam according to claim 1 wherein the foam propellant is taken from the group comprising hydrocarbons and fluorocarbons.

9. An aerosol foam according to claim 8 wherein the hydrocarbons are incorporated in a proportion of about 5.50%.

10. An aerosol foam according to claim 8 wherein the fluorocarbons are incorporated in a proportion of about 9.5%.

93-047146/06 A96 B07 D21 **PROM- 91.06.05**
SOC PROMOTION RECH & INNOVATION *FR 2677369-A1
91.06.05 91FR-006827 *(92.12.11)* C09K 3/30, A61K 7/00, 9/12

Aerosol foam compsns. for pharmaceutical or cosmetic use - contg. self-emulsifying wax emulsifier and propylene glycol solvent
C93-021205

Addnl. Data: SUCK C, BRET P, POZZI J

A(12-V1, 12-V4) B(4-B1C, 4-C3C, 10-E2, 10-E4C, 10-G2, 10-H2, 10-J2, 12-M1A) D(8-B10)

Aerosol foam compsns. useful as carriers for pharmaceutical or cosmetic ingredients comprise an emulsifier and a solvent, where the emulsifier is a self-emulsifying wax (I) and the solvent is propylene glycol (II).

USES

The compsns. may be used for topical admin. of liposomes, antibiotics, corticosteroids, antiparasitic agents, antiinflammatory agents, antiinfectious agents, antiseptics, etc.

ADVANTAGES

The compsns. have good stability and contain only pharmacologically and cosmetically acceptable ingredients.

PREFERRED COMPOSITIONS

Nonaqueous compsns. contain another emulsifier, esp. ethoxylated stearyl alcohol (III). Aq. compsns. contain water and another emulsifier, esp. 'Polysorbate 20' (IV).

The compsns. also contain a fatty acid glyceride, polyethylene glycol, preservatives (esp. methyl and propyl paraben), and either 5.5% of a hydrocarbon propellant or 9.5% of a fluorocarbon propellant.

Nonaqueous compsns. contain 2.7-7.81% emulsifiers, 92.19-97.3% (II) and 0.14% preservatives.

Aq. compsns. contain 3.52-4.35% emulsifiers, 42-64.16% (II), 31.99-54.04% water and 0.14% preservatives.

EXAMPLE

An aq. compsn. comprises 1.76% (I), 1.76% (IV), 42.38% (II), 21.69% glyceride/polyethylene glycol, 32.27% water, 0.12% methyl paraben, 0.02% propyl paraben and 5.5% butane.(7pp367DAHDwgNo0/0).

FR2677369-A

(19) RÉPUBLIQUE FRANÇAISE

INSTITUT NATIONAL
DE LA PROPRIÉTÉ INDUSTRIELLE

PARIS

(11) N° de publication : **2 677 369**
(à n'utiliser que pour les commandes de reproduction)

(21) N° d'enregistrement national : **91 06827**

(51) Int Cl[5] : C 09 K 3/30; A 61 K 9/12, 7/00

(12) DEMANDE DE BREVET D'INVENTION A1

(22) **Date de dépôt** : 05.06.91.

(30) **Priorité** :

(43) **Date de la mise à disposition du public de la demande** : 11.12.92 Bulletin 92/50.

(56) **Liste des documents cités dans le rapport de recherche** : *Se reporter à la fin du présent fascicule.*

(60) **Références à d'autres documents nationaux apparentés** :

(71) **Demandeur(s)** : *SOCIETE DE PROMOTION, RECHERCHE ET INNOVATION TECHNOLOGIQUE (Société Civile)* — FR.

(72) **Inventeur(s)** : Suck Catherine, Bret Pierre et Pozzi Jacques.

(73) **Titulaire(s)** :

(74) **Mandataire** : Cabinet Pierre Loyer.

(54) Mousse aérosol.

(57) Mousse-aérosol utilisable comme vecteur de principes actifs médicamenteux ou cosmétiques.

Elle comporte en association un émulsifiant et un solvant, l'émulsifiant étant une cire auto-émulsifiante, et le solvant étant le propylène glycol.

FR 2 677 369 - A1

MOUSSE AEROSOL

L'invention concerne une mousse-aérosol utilisable comme vecteur de principes actifs médicamenteux ou cosmétiques.

Pour le traitement de certaines affections, il est préférable d'utiliser des produits topiques, et pour l'application de ces produits, une mousse-aérosol constitue un vecteur présentant certains avantages, en raison de la disponibilité des molécules de principes actifs qui y sont mises soit en solution, soit en suspension.

La présente invention a pour objet une mousse-aérosol utilisable comme vecteur de principes actifs médicamenteux ou cosmétiques, caractérisée en ce qu'elle comporte en association, un émulsifiant et un solvant, l'émulsifiant étant une cire auto-émulsifiante, et le solvant étant le propylène glycol.

Selon d'autres caractéristiques de l'invention ;

- dans le cas d'une mousse non aqueuse, elle comporte en outre un autre émulsifiant tel que l'alcool stearylique polyoxyéthylène ;
- dans le cas d'une mousse aqueuse, elle comporte en outre un autre émulsifiant tel que le polysorbate 20, et de l'eau ;
- elle comporte en outre un glycéride d'acides gras et de polyéthylène glycol ;
- elle comporte des agents de conservation comme le parahydroxybenzoate de méthyle et parahydroxybenzoate de propyle ;
- dans le cas de mousses non aqueuses, les proportions des constituants sont les suivantes :
  - . émulsifiants : entre 2,70 et 7,81%
  - . solvant : entre 92,19 et 97,30%
  - . agents de conservation : environ 0,14%
- dans le cas de mousses aqueuses, les proportions des constituants sont les suivantes :
  - . émulsifiants : entre 3,52 et 4,35%
  - . solvant : entre 42,00 et 64,16%
  - . eau : entre 31,99 et 54,04%

. agents de conservation : environ 0,14%

- l'agent de propulsion de la mousse est pris dans le groupe des hydrocarbures et des carbofluorés ;

- les hydrocarbures sont incorporés dans la proportion d'environ 5,50%

- les carbofluorés sont incorporés dans la proportion d'environ 9,5%.

Des exemples de réalisation de mousses-aérosols selon l'invention sont donnés dans le tableau annexé. Dans ce tableau, les compositions A1 à A7 sont des compositions aqueuses, et les compositions NA1 à NA7 des compositions non aqueuses.

Dans toutes les compositions :

- l'émulsifiant 1 est une cire auto-émulsifiante,

- le solvant est le propylène glycol

- l'agent de conservation PHBM est le parahydroxybenzoate de méthyle,

- l'agent de conservation PHBP est le parahydroxybenzoate de propyle,

- l'agent propulseur 1 est le butane.

Dans les compositions aqueuses :

- l'émulsifiant 2 est le polysorbate 20,

- le glycéride est un glycéride d'acides gras et de polyéthylène glycol,

- l'agent propulseur 2 est un fréon.

Dans les compositions non aqueuses ;

- l'émulsifiant 2 est l'alcool stéarylique polyoxyéthylène.

Les compositions moussantes selon l'invention présentent plusieurs avantages et en particulier :

- elles sont très stables ;

- les constituants utilisés sont tous acceptés par les législations pharmaceutique et cosmétique ;

- elles peuvent accepter jusqu'à 30% en poids de principes actifs médicamenteux ou cosmétiques, tels que des liposomes, des antibiotiques, des corticoïdes, des antiparasitaires, des anti-inflammatoires, des anti-infectieux, ou des antiseptiques, par exemple ;

- elles sont particulièrement bien adaptées pour les applications de produits topiques.

TABLEAU

Aqueuse	A1	A2	A3	A4	A5	A6	A7
Emulsifiant 1	1,76	1,76	1,76	1,76	1,77	2,61	2,18
Emulsifiant 2	1,76	1,76	1,76	1,76	1,77	1,74	1,74
Solvant	42,38	53,30	64,16	42,44	48,23	42,01	42,00
Glycéride	21,69					21,50	21,49
Eau	32,27	43,18	32,32	54,04	48,23	31,99	31,99
PHBM	0,12	0,12	0,12	0,12	0,12	0,12	0,12
PHBP	0,02	0,02	0,02	0,02	0,02	0,02	0,02
Propulseur 1	5,50	5,50	5,50	5,50	5,50		
Propulseur 2						9,47	9,51

Non aqueuses	NA1	NA2	NA3	NA4	NA5	NA6	NA7
Emulsifiant 1	1,25	1,56	1,01	0,83	0,54	1,25	1,04
Emulsifiant 2	4,99	6,25	4,04	3,32	2,16	5,00	4,17
Solvant	93,62	92,19	94,18	95,71	97,30	93,75	95,00
PHBM	0,12	0,12	0,12	0,12	0,12	0,12	0,12
PHBP	0,02	0,02	0,02	0,02	0,02	0,02	0,02
Propulseur 1	5,50	5,50	5,50	5,50	5,50	5,50	5,50

REVENDICATIONS

1. Mousse-aérosol utilisable comme vecteur de principes actifs médicamenteux ou cosmétiques, caractérisée en ce qu'elle comporte en association, un émulsifiant et un solvant, l'émulsifiant étant une cire auto-émulsifiante, et le solvant étant le propylène glycol.

2. Mousse-aérosol selon la revendication 1, caractérisée en ce que dans le cas d'une mousse non aqueuse, elle comporte en outre un autre émulsifiant tel que l'alcool stearylique polyoxyéthylène.

3. Mousse-aérosol selon la revendication 1, caractérisée en ce que dans le cas d'une mousse aqueuse, elle comporte en outre un autre émulsifiant tel que le polysorbate 20, et de l'eau.

4. Mousse-aérosol selon la revendication 3, caractérisée en ce qu'elle comporte en outre un glycéride d'acides gras et de polyéthylène glycol.

5. Mousse-aérosol selon la revendication 1, caractérisée en ce qu'elle comporte des agents de conservation comme le parahydroxybenzoate de méthyle et parahydroxybenzoate de propyle.

6. Mousse-aérosol selon l'ensemble des revendications 2 et 5, caractérisée en ce que dans le cas de mousses non aqueuses, les proportions des constituants sont les suivantes :

- émulsifiants : entre 2,70 et 7,81%
- solvant : entre 92,19 et 97,30%
- agents de conservation : environ 0,14%

7. Mousse-aérosol selon l'ensemble des revendications 4 et 5, caractérisée en ce que dans le cas de mousses aqueuses, les proportions des constituants sont les suivantes :

- émulsifiants : entre 3,52 et 4,35%
- solvant : entre 42,00 et 64,16%
- eau : entre 31,99 et 54,04%
- agents de conservation : environ 0,14%

8. Mousse-aérosol selon la revendication 1, caractérisée en ce que l'agent de propulsion de la mousse

est pris dans le groupe des hydrocarbures et des carbofluorés.

9. Mousse-aérosol selon la revendication 8, caractérisée en ce que les hydrocarbures sont incorporés dans la proportion d'environ 5,50%

10. Mousse-aérosol selon la revendication 8, caractérisée en ce que les carbofluorés sont incorporés dans la proportion d'environ 9,5%.

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DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie	Citation du document avec indication, en cas de besoin, des parties pertinentes	Revendications concernées de la demande examinée
X	WORLD PATENTS INDEX LATEST Derwent Publications Ltd., London, GB; & ZA-A-8 403 016 (WRIGHT) 17 Octobre 1984 * abrégé *	1,4,8,9, 10
Y	FR-A-2 647 344 (PHYSIOPHARM.) 30 Novembre 1990 * revendications 1,3,4; exemple 1 *	1,2,3,8, 9,10
Y	FR-A-2 154 959 (AIR LIQUIDE) 18 Mai 1973 * revendications 1,5,7,9; exemple 3 *	1,2,3,8, 9,10
A	WORLD PATENTS INDEX LATEST Derwent Publications Ltd., London, GB; & JP-A-62 016 411 (POLA KASEI KOGYO) 24 Janvier 1987 * abrégé *	1,2,8,9, 10
A	US-A-3 384 541 (CLARK) 21 Mai 541 * colonne 2, ligne 59 - colonne 3, ligne 16; revendication 1 *	1,2,8,9, 10
A	US-A-4 515 810 (CHOW) 7 Mai 1985 * abrégé; revendications 1,3 *	1-10
A	US-A-3 092 555 (HORN) 4 Juin 1963 * abrégé *	1-10

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CATEGORIE DES DOCUMENTS CITES

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(54) Title: PHARMACEUTICAL COMBINATONS COMPRISING A FUNGICIDE, A BACTERIOSTATIC SULPHONAMIDE AND AN ANTIBACTERIAL COMPOUND FOR TOPICAL APPLICATION

(57) Abstract: Medical combination and its method of topical use comprising active ingredients which are sparingly soluble in water, preferably in one single composition against microbes which are pathogenic in humans and animals and which usually appear together. It comprises at least one active ingredient which is effective against several of the opportunally pathogenic strains of the group consisting of *fungi* Candida, Aspergillus, and/or Fusarium, and aerobic *bacteria*: Gram-negative bacilli such as Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus, Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species and Mycobacterium species such as Mycobacterium ulcerans, *microbes* similar to bacteria of the Chlamydia species such as Chlamydia trachomatis. To be used for treatment of the skin or mucous membranes bearing epithelial lesions, deficiency or injuries and to be used in body cavities to prevent or cure infections and deficiencies. The composition contains - dispersed in a carrier which is pharmaceutically acceptable on the site of treatment - at least one fungicide, which is preferably azole or polyene type and at least one antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and at least one bacteriostatic sulphonamide. Additionals mainly for use on skin may include zinc oxide and asulene. Useful in forms of ointment, tablet, effervescent tablet, suppository, foam.

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PHARMACEUTICAL COMBINATIONS COMPRISING A FUNGICIDE, A BACTERIOSTATIC SULPHONAMIDE AND AN ANTIBACTERIAL COMPOUND FOR TOPICAL APPLICATION

Subject of the invention is a medical combination preferably in one single composition against microbes which are pathogenic in humans and animals and which appear together or which represent a danger to appear together, said composition to be topically used for human or veterinary treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries or to be used in body cavities to prevent or cure infections, said combination comprising as active ingredients fungicidally and antibiotically acting compounds and a sulphonamide together. According to a preferred and typical aspect of the invention the combination contains as active ingredients a fungicide, an antibiotic and a bactericidal sulphonamide together.

The invention comprises a combination containing at least one active ingredient which is effective against several of the fungal, bacterial and other microbe strains of the group consisting of *fungi* Candida, Aspergillus, Fusarium genus, *other microbes* such as Chlamydia genus, and *bacteria* such as aerobic bacteria: Gram-negative bacilli, Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci, such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus, Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species and mycobacterium species such as Mycobacterium ulcerans. The above microbes are opportunally pathogenic in humans and animals.

It is one of the basic ideas of our invention to seize the above spectrum with one medical combination, preferably one composition. To achieve this goal according to the invention the combination comprises active ingredients which are sparingly soluble in water at 20 to 100 °C (< 50 µg/ml at room temperature). Generally the presence of three types of active ingredients is necessary: a fungicide, an antibiotic and a sulphonamide; however subject to

the mechanism of activity it might exceptionally be possible that only two active ingredients are sufficient to cover the range of microbes envisaged. Such variations are also considered to represent part of the present invention.

The drug according to the invention thus

a) comprises the combination of active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment and which ensure the combination of three biological effects and which include together
   i) at least one fungicide, which is preferably of the azole or polyene type and
   ii) at least one antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and
   iii) at least one bacteriostatic sulphonamide,
b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment
c) and where the mass ratio of said active ingredients amounts to i : ii : iii = 0,1 - 10 : 0,1 - 10 : 10 - 200 whereby the ratio of the carrier is about 80 - 99 mass%.

The combination preferably appears in one single composition. The invention however also includes those accomplishments, where the different types of active ingredients appear in several compositions ready to be used in combination according to the invention. Without the intention of limitation in the following we mainly elucidate that aspect of the invention where the combination is comprised in one single composition.

Abbreviations and definitions used in the specification:

MIC = minimal effective concentration. At this concentration of the test material the microbe does not proliferate at test conditions.

It is known that external ulcers (in the first line the crural ulcers) rather differ in their origin however on the course of their treatment the arising complications might be similar. ("Bacterial population of chronic crural

ulcers: is there a difference between the diabetic, the venous and the arterial ulcer?" VASA 2000; 29:62-70). Their healing is slow and cumbersome.

In treatment of external ulcers at early stadium with open wounds or discharge a light gauze bandage is generally applied. For the treatment of ulcers covered with a necrotic tissue it was proposed to use a bandage soaked with sterile salt solution and changing 3 - 4 times a day. ("Up-to-date Medical Diagnostics and Therapy" Officina Nova 1990. pages 1160 to 1166). In case of burns the first treatment means cooling of the wound and fluid replacement followed by alleviation of pain.

It is characteristic for burns that the destructed or dead tissues remain on place and thus their treatment needs special methods. It was traditional to initiate angiogenesis by artificially causing inflammation which was effected after waiting for several days while the danger of uncontrollable surface infection and pain was significally increased. On the surface there appeared a thick, armour-like layer of scar (of 1-1,5 cm thickness) and if this was on the chest it was necessary to ensure respiration surgically while complete akinesia appeared often in the regions of the joints.

External ulcers are caused generally by circulatory failure, or mechanical effects. In the ambience of several years old ulcers the collateral vessels (which are very important for ulcer healing) are often in a ruined state.

The decubitus (bed-sore) is a specific type of ulcers which is the result of insufficient blood supply and metabolic disturbances caused by the long lasting effect of pressure on the skin covering a bony or chondrous base. The mostly affected places are the skin parts covering the sacrum and the hip, however there is a possibility of a decubitus also on the skin of the occipital region, the ears, the elbows, the heels and the ankles. It is observed most frequently on aged, weak, paralysed or unconscious patients. The ulcer might be infected on the surface.

There are several methods used to treat the decubitus. Only the first symptoms can be treated locally with powders containing antibiotics and with plaster-like absorbent bandages (Gelfoam°). When the wound is clean, a hy-

drocolloid bandage such as e.g. DuoDerm° can be applied. To treat a developed incubitus surgery, cleaning of the wound, washing, stable bandages containing 1 % iodine-chloroxychinolinum° [Vioform°] mixed into Lassar paste were used together with foam pillows under the patient. Local antiseptics were generally not recommended; instead systemic oral or parenteral antibiotic treatment was used for deep infections. (Current Medical Diagnosis & Treatment, 1996 by Appleton & Lange, page 146.)

Symptoms of ulcer caused by venous circulatory failure appear often at the medial side of the crurum over the malleolus accompanied by crural oedema, varicositas, hyperpigmentation, red-coloured peeling territories and scars of old ulcers. Ulcers are often preceded by red, scratching spots of stasis dermatitis.

As local treatment compression was suggested together with cleaning of the wound with salt solutions; the yellow scars containing fibrin were removed with scissors optionally under local anaesthesia. Clean ulcers were treated with gels of metronidazole to inhibit growth of Gram-negative bacteria and limit the odour. The red, inflamed parts of the skin were covered with strong or middle strong steroid ointments. Thereafter the wound was covered with an occlusive hydroactive bandage (Duoderm° or Catinova°) or polyurethane foam (Allevyn°), followed by the use of zinc boots which were changed weekly. Epidermal cell culture grafts, laser and biotron lamp irradiation represent new techniques.

As systemic antibiotics oral dicloxacillin°, or ciprofloxacin was suggested. (Current Medical Diagnosis & Treatment, 1996 by Appleton & Lange, page 147.)

For treatment of burns and external ulcers also such ointments were suggested (int. publication N° WO98/44914) which contained as active ingredients one or more sulphonamides, macrolide antibiotics, chloramphenicol or thiamphenicol and zinc oxide, camomille oil and azulene. Specific examples were published on mixtures containing as the antibiotic chloramphenicol, primycin sulphate, as the sulphonamide sulfadimidine, sulfamethoxazole and as further ingredients vaseline and wax, camomile oil, zinc oxide and azulene. It was the disadvantage of the product that primy-

cin sulphate with a stable quality and composition is not available on the market and further that application of the drug in cases combined with fungous infections is limited by the restricted fungistatic effect of primycin or chloramphenicol. A further drawback lies in that the applied bacteriostatic agents were not specific on the micro-organisms which appear most frequently in ulcers and burns; thus an excess of antibiotics had to be administered to achieve the adequate bacteriostatic effect. Yet: marketing on a pharmacy level indicates encouraging results when applying the drug containing primycin. It is one aim of the present invention to eliminate the above drawbacks of this known drug, to provide a pharmaceutical which meets the requirements of modern drug health registration and also better approaches the curative aim. A further aim is to broaden the field of applicability.

For epithelial injuries, mainly burns, an ethanol plant extract spray is marketed which ensures success without using bandages (Irix®, Naksol® of Human, USP 4601905; USP 4466961). However the presence of ethanol causes transitional pain and this represents a drawback in use.

It is the main aim of the present invention to provide a local medicament for attending ulcers and burns which is exempt of the above drawbacks and which is effective against all microbes threatening the wounds, which is not absorbed but to the extent as necessary (and thus does not load the whole organism), which does not cause pain, and which leaves but a minimum a traces after recovery (thus avoiding plastic surgery).

Most frequent complication related to wounds is infection of the wound surface which may cause an endotoxemic shock or even sepsis. The injured surface of the skin is not able anymore to maintain its barrier function and thus the invasion of pathogenic microbes gradually increases. Gram negative and Gram positive bacteria and fungi can be found. On the course of treatment of burns more than thousand pathogens were isolated which had caused smaller or bigger complications. In the case of external ulcers more than 170 pathogens were isolated the bigger part of which overlapped with the pathogens found in burns though the ratio of anaerobic bacteria was higher here (1984; 1999).

We first clarified what sort of microbes we have to fight against. According to literature of years 1998 to 2000 the enlisted microbes were isolated from burns (mainly large wounds related to more than 50 % of the body surface). Out of these only Candida and Mucor species were isolated from external ulcers (1988). Such types of microbes are demonstrated which are the most frequent or which represent a larger group of opportunal pathogens (1998, 1992; 1973; 1997).

Fungi:

Candida tropicalis	Aspergillus flavus
Candida parapsilosis	Aspergillus fumigatus
Candida albicans	Aspergillus terreus
Torulopsis (Cand.)glabrata	Aspergillus niger
Fusarium oxysporum	Mucor spp
Trichosporon beigelii	Rhizopus spp
	Penicillium spp

Other microbes: Chlamydia trachomatis

Bacteria:

Aerobic bacteria:

Gram-negative bacilli
Proteus mirabilis
Proteus vulgaris
Pseudomonas aeruginosa
Enterobacter aerogenes
Enterobacter faecalis
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca
Serratia marcescens
Citrobacter spp
Aeromonas spp

Gram-negative cocci:
Neisseria meningitidis
Neisseria spp
Acinetobacter anitratus

Anaerobic bacteria:

Gram-negative cocci:
Bacteroides fragilis
Bacteroides ovatus
Bacteroides spp
Fusobacterium mortiferum
Fusobacterium mucleatum

Gram-positive cocci:
Peptococcus magnus
Peptococcus assaccharoliticus
Peptostreptococcus anaerobius
Peptostreptococcus micros

Gram-positive bacilli:
Clostridium welchii
Clostridium perfingens
Clostridium spp
Propionibacterium acnes
Eubacterium lentum
Mycobacterium ulcerans

Gram-positive bacilli:
Corynebacterium spp
Bacillus sphaericus

Gram-positive cocci:
Group D Streptococcus
Staphylococcus aureus
Streptococcus pyogenes
Streptococcus faecalis
Streptococcus spp

A further subject of the present invention is the treatment of cavities of the body including the renal and the vaginal cavities and those which are the subjects of the field of bacteria and fungi which are responsible for sexually transmitted diseases in humans and other mammals. Some are already present in the above list including i.a. the following:

Neisseria gonorrhea
Trepponema pallidum
Haemophylus ducreyi
Chlamydia trachomatis.

Knowing the above we studied to what extent the drugs used up to now covered the above spectrum while also meeting the other requirements. We did not encounter such antibiotic which alone would be sufficiently effective against Gram-positive, Gram-negative bacteria and fungi while appropriately entering the wound and not causing pain. Silver-sulfadiazine is a drug which is widely used for burns however it does not represent an appropriate protection against certain Pseudomonas strains and besides may cause fever, leukopenia while slowing epithelization. Mafenide is effective against Pseudomonas but its use causes pain and it slows down recovery of burn wounds. Iodine-povidone is effective against both Gram-negative and Gram-positive bacteria and fungi but it scarcely enters the scars, its use is painful and it dries the wound out. Amphotericin B is a wide spectrum antifungal which is used in mycosis appearing in relation to burn injuries both systemically and locally. However its strong cytotoxic effect causes considerable side effects; when used locally also skin irritation occurs (1991). Nystatin is a good

means against Candida in burns and other infections however it is but slightly acting on Aspergillus and Mucor species (1982). It was also suggested to apply streptomycin, fradiomycin sulphate, kanamycin, chloramphenicol, tetracyclin (JP 54 140712) and for external ulcers with progressed infections dicloxacycline and clindamycin. The spectrum of effectivity of all these does not cover completely the microflora of the ulcers. Ointments containing bacitracin and neomycin were also used; however bacitracin is not effective against Gram-negatives and in the case of neomycin resistance is frequent (1990). It is also known that certain azalides (azithromycin, clarithromycin and other) are effective i.a. against certain streptococci, Chlamydia pneumoniae, Chlamydia trachomatis. Azithromycin and clarithromycin were orally used to treat complicated skin infections in Streptococcalis pharyngitis (Current Medical Diagnosis & Treatment, 1996 by Appleton & Lange, page 1336).

We consider of key importance long lasting and effectful defence against the fungi present. Some of the fungi - for instance some of those belonging to the genus Candida - represent part of the normal healthy human and animal microflora. Candida albicans can be isolated from the oral cavity, faeces and vagina of most healthy persons. However opportunally they are pathogens in the areas considered - influencing noxiously and even inhibiting healing and epithelization specifically of ulcers and burns.

It is also our aim to avoid that local administration of strong antibacterial agents represents a danger on the organism as regards resistance and thus we decided to avoid absorption of these substances.

It is a further aim of the invention to ensure good applicability of the medicament for veterinary purposes. Specifically the effectful burn and ulcer treatment of use animals, house and bred animals has a considerable economic impact on both the health of the animals and the quality of the products (meat, leather, wool). To achieve these needs again a composition which is not absorbed and does not cause animal resistance or even human resistance in the case of animals marked for slaughter.

One main aspect of the present invention is the combination of such antibacterial compounds the effective spectrum of which covers in the possible best manner the range of the above pathogens and thus reduces the danger of infection to a minimum on the course of healing while it is not dissolved in water; it does not reduce the activity of other antibiotics which are parallel systhemically administered into the organism to treat other clinical patterns; it can be homogenised in the selected carriers and is stable (shelf life at least 2 years). This can suitably be used in such known (international publication document N° WO98/44914) water-free oil based suspension, emulsion or solution, ointment, which enhances scar-free or minimal scar healing of the injuries.

The combination and composition described as the object of the present invention in the first part of this specification meets these requirement.

Thus one aspect of the present invention is a synergistic multicomponent drug. It is basically important that as active ingredients it contains components which are sparingly soluble in water at 20-100 °C (< 50 µg/ml at room temperature). This means that the strongly effective active ingredients are restricted territorially to the region of application though when starting treatment the composition is also contacted with open wounds.

One component is an antifungal compound acceptable in human or veterinary medication preferably an azole or a polyene type fungicide selected of those according to the invention which are effective against the following: opportunally pathogenic fungus strains belonging to the families Candida, Aspergillus and/or Fusarium. A specifically preferred embodiment of the combination according to the invention contains as one or more fungicide compounds effective against several members of the opportunally pathogenic strains of the following fungi: Candida tropicalis, Candida parapsilosis, Candida albicans, Torulopsis (Cand.) glabrata, Fusarium oxysporum, Trishosporon beigelii, Aspergillus flavus, Aspergillus fumigatus, Aspergillus terreus, Aspergillus niger, Mucor spp, Rhizopus spp, Penicilium spp and/or Chlamydia trachomatis.

"Azoles" mentioned above differ in their structure but as regards antifungal activity they show similarities and their spectrum of activity meets our requirements according to the present invention. They are not soluble in water and are effective against Candida and Aspergillus species (1986; 1984). Preferably applicable are members of the group miconazole, itraconazole, econazole, ketoconazole, fluconazole. Miconazole is considered to be specifically advantageous because the danger of cross resistance is the least.

From the group of fungicide compounds natamycin, nystatin and/or naftitin are considered to be preferable according to the invention. Natamycin is effective against numerous fungous infections of the skin and naftitin is known to be a successfully used external fungicide thanks to its broad spectrum of activity while it is not related to other fungicides.

The second basic component of the combination according to the invention is a water-insoluble antibacterial composition comprising one or more antibacterial ingredients which are effective against preferably several members of the following opportunally pathogenic bacterium strains:
aerobic bacteria: Gram-negative bacilli, Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci, such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus, Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species and mycobacterium species such as Mycobacterium ulcerans, Neisseria gonorrhea, Trepponema pallidum, Haemophylus ducreyi, and/or other bacterium-like microbes such as Chlamydiae, specifically Chlamydia trachomatis.

Such conditions are met according to the present invention by macrolide, azalide, linkozamide, polypeptide type antibiotics.

Preferred macrolids are: erythromycin, roxythromicin, and their derivatives. Preferred azalides are e.g. azithromycin, clarithromycin, clindamicin, clyncomycin. Azithromycin is considered specifically advantageous because it is also effective against most of the anaerobic species (1995), does not cause cross resistance, shows an effect already in relatively small doses based on our MIC studies and can be synergized (see Examples I.1 and I.2).

Amongst the polypeptide type antibiotics tyrothricin, magainin, cecropin are highly preferred. Several of the polypeptide type antibiotics show not only an antibacterial (both Gram positive and Gram negative) effect but also have antifungal qualities. According to the present invention several polypeptide type antibiotics now in development are potential and effective active ingredients of the combinations according to the present invention.

The above fungicides and antibiotics are generally marketed in the form of their water-soluble salts so as to ensure the appropriately effective serum levels. According to the present invention however water-insoluble, hydrophobic forms are used. This ensures that the active ingredient is not absorbed in its unchanged form into the systemic circulation at the site of treatment. Instead it remains on place in such concentration which ensures its microbicide effect at the area of treatment until its enzymatic decomposition.

The further active ingredient of the combination according to the invention is a bacteriostatic sulphonamide. Preferred are sulfadimidine and/or sulfamethoxazole in their water insoluble forms.

It is a further basic recognition according to the present invention that in case of simultaneous presence of the fungistatics and bacteriostatics which are considered necessary synergism was observed between several members of the relative groups: the combinations show an effect which is more than the expected additive effect.

This synergism is exemplified with the fungicide miconazole, the antibiotic azithromycin, the sulphonamide sulfamethoxazole in a common ointment, using as the test organism a Staphylococcus aureus which in cases of ulcers

represents one of the most frequently attacking microbe (see Example I.2). Comparing the MIC values (mg/ml) of such ointments which contained only one or two of the 3 active ingredients (in any of the pairs) it was found that in the case of the tested Staphylococcus aureus ATCC 6538 the smallest MIC value was measured for ointments containing all three active ingredients together.

Preferable combinations of the active ingredients showing an expressed synergistic effect are those where the mass ratio of the three ingredients azithromycin : miconazole : sulfamethoxazole amounts to 0,5 - 1,5 : 0,5 - 1,5 : 90 - 190 preferably about 1 : 1 : 140. In the case of ointments a preferred composition is for example the following: azithromycin 0,02 mass%, miconazole 0,02 mass%, sulfamethoxazole 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,12 mass%, preferably in the form of aetheroleum camomillae and/or aetheroleum millefolii.

In the compositions according to the invention the active ingredients are embedded in carriers. The carrier ensures uniform dispersion and localisation of the actives in the desired region until exertion of their effect.

Such compounds can be used as carriers which area pharmaceutically acceptable at the site of the treatment and thus do not damage the open wounds or the cavities of the body and their mucous membranes.

According to the invention the active compounds are dispersed in the carrier in the most uniform manner and are thus in the form of stable solutions, suspensions or emulsions.

The quantity of the carrier in the composition amounts to about 80 - 99 mass% and depends on the type of formulations and packaging in which the specific composition appears and is applied. Compositions appearing in the form of ointments comprise preferably 85 - 95 mass% of the carrier, oily compositions appearing as spray formulations contain about 90 - 98 mass% of the carrier while foam compositions contain suitably 95 - 99 mass% of the carrier.

Preferred formulations of the compositions are ointments and sprays. Suitable carriers are at least one pharmaceutically on the site of treatment acceptable water-immiscible plant or mineral oil, fat and/or wax. Thus for

example vaseline, lanalcol, cetyl stearate and/or beeswax are suitable carriers. The applied active ingredients and possible auxiliaries present are dissolved, suspended or emulgated in the carrier so as to ensure the uniform dispersion and besides avoiding unwanted absorption into the direction of the sub-dermal layers or into the systemic circulation. Spray formulations usually also contain a siloxane type solvent such as hexamethyldisolaxane.

The pharmaceutical product according to the invention can appear preferably in the form of one single composition and formulation suitably corresponding to the ointment, foam or spray form actually chosen. It is also possible to market and apply the drug in several formulation forms however to do this it is imperative to ensure that the ratios are the prescribed ones and stay unchanged. Thus the invention also encompasses those embodiments where compositions and/or formulations are such that for instance the compositions according to the invention containing only the antibacterial or only the antifungal active ingredient respectively can be administered from separate tubes or vessels parallel or subsequently according to an exact protocol.

Such solutions might also be adequate in the late period of healing when the constant treatment with antibiotics might not be anymore necessary to accomplish the healing process but the constant presence of all other ingredients has to be continuously provided.

A further possible formulation of the compositions according to the invention for treatment of both exterior wounds and body cavities are the foam preparations. This formulation is marketed and used in flasks which are sufficiently equipped to ensure that a sufficient amount of the composition be administered unto the surface of the region to be treated. Optionally a power gas is used for this purpose. When the composition reaches the surface it solidifies as a foam which then collapses and forms a uniform protective layer which ensures the presence of the active ingredients in the ambience of the wound. This form contains as carriers such materials which solidify as a foam and which at the region of application correspond to the pharmaceutical regulations and which is capable to

dissolve, suspend and/emulgate both in liquid and in solid form the compounds present.

Preferred carriers of foam compositions are for instance polysiloxanes and/or oligosiloxanes and optionally as power gas air, nitrogen, inert gas.

A further object of the invention (as sub-groups of the compositions disclosed above) are combinations preferably in one single composition to be used for human or veterinary treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries of the living skin, external ulcers, burn injuries, necroses caused by irradiation, wounds (in the following "wounds") to prevent or cure infections, to restore the epithelium

a) said composition comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment

i) a fungicide, which is preferably of the azole or polyene type and

ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and

iii) a bacteriostatic sulphonamide and

iv) an active ingredient promoting circulation of the blood and body fluids preferably azulene or guaiazulene and

v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide

b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 whereby the ratio of the carrier amounts to about 80 - 99 mass%.

These compositions are specifically advantageous in the treatment of external burns, ulcers (crural ulcers, decubitus) and for restoration of the epithelium. It was found to be specifically advantageous both as regards maximal avoidance of cross resistance and to achieve quick healing of the wounds to use the following composition: azithromycin 0,01 - 1,5 mass% preferably 0,02 mass%,

miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% preferably in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax.

The use of azulene and zinc oxide was already proposed earlier in ointments for treatments of wounds of the skin (WO98/44914). Application of these materials is possible also in case of the combination according to the present invention without loosing the synergistic effect (see Examples I.1 and I.2).

Further subjects of the present invention are the combinations preferably in one single composition to be used for human or veterinary treatment of cavities of the body such as the vagina, the rectum or their epithelium, their mucous membranes, to prevent or to cure infections, to restore the epithelium

a) said composition comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment

i) a fungicide which is preferably azole or polyene type and

ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and

iii) a bacteriostatic sulphonamide,

iv) an active ingredient promoting circulation of the blood and body fluids preferably azulene or guaiazulene,

v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide

b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 whereby the ratio of the carrier is about 80 - 99 mass%.

A preferred composition of this use form is the synergistic composition comprising the following: azithromycin, erythromycin or clindamycin 0,01 - 1,5 mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc-oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% preferably in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax.

These appear preferably in the form of tablets, dragées, suppositories, foam material, oily suspensions, solutions or emulsions for spraying comprised in adequate compositions, dosage units and packaging. They also contain the corresponding further auxiliary additives to these forms. For treatment of cavities a suppository comprising as a carrier adeps solidus 50 and/or a triglyceride is preferable.

The composition according to the invention may optionally comprise as a further additive a pharmaceutically acceptable colouring agent, a perfume, a volatile oil. This might be useful in paediatric treatment though even in absence of these the products do not have any unpleasant odour or appearance. Further additives include stabilizers or puffers, such as e.g. adipic acid, malic acid, oleic acid, succinic acid, tartaric acid, boric acid lactic acid etc.

Subject of the present invention are further methods of treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries or to be used in body cavities to prevent or cure infections in humans or animals against pathogenic microbes which appear together or which represent a danger to appear together comprising the local application of a combination comprising at least one active ingredient which is effective against several of the opportunally pathogenic fungal and bacterial strains of the group consisting of fungi Candida, Aspergillus, Fusarium genus fungi, and
aerobic bacteria: Gram-negative bacilli, Proteus, Pseudomonas, Chlamydia and/or enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aero-

monas; Gram-negative cocci, such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus, Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species, mycobacterium species such as Mycobacterium ulcerans, bacterium-like other microbes of the Chlamydia species such as Chlamydia trachomatis.

Specifically successful are those methods of treatment where the applied combinations comprise at least one active ingredient which is effective against several of the following opportunally pathogenic microbes: Candida tropicalis, Candida parapsilosis, Candida albicans, Torulopsis (Cand.) glabrata, Fusarium oxysporum, Trishosporon beigelii, Aspergillus flavus, Aspergillus fumigatus, Aspergillis terreus, Aspergillus niger, Mucor spp, Rhizopus spp, and/or Penicilium spp or where the applied combinations comprise at least one active ingredient which is effective against several of the following opportunally pathogenic microbes: *Aerobic bacteria*: Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Enterobacter aerogenes, Enterobacter faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Citrobacter spp, Aeromonas spp, *Gram-negative cocci*: Neisseria meningitidis, Neisseria spp, Acinetobacter anitratus, *Gram-positive bacilli*:, Corynebacterium spp, Bacillus sphaericus, *Gram-positive cocci*: Group D Streptococcus, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus faecalis, Streptococcus spp, *Anaerobic bacteria*: *Gram-negative cocci*: Bacteroides fragilis, Bacteroides ovatus, Bacteroides spp, Fusobacterium mortiferum, Fusobacterium mucleatum *Gram-positive cocci*: Peptococcus magnus, Peptococcus assaccharoliticus, Peptostreptococcus anaerobius, Peptostreptococcus micros, *Gram-positive bacilli*:, Clostridium welchii, Clostridium perfingens, Clostridium spp, Propionibacterium acnes, Eubacterium lentum and or other mi-

crobes of the Chlamydia genus such as Chlamydia trachomatis.

The method of treatment is accomplished by topical application on the place of the injury in an effective dose corresponding to the injury the combination according to the invention preferably in one single composition

a) comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment

i) a fungicide, which is preferably azole or polyene type and

ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and

iii) a bacteriostatic sulphonamide,

b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii = 0,1 - 10 : 0,1 - 10 : 10 - 200 whereby the ratio of the carrier is about 80 - 99 mass%.

Specifically successful are methods where synergistic compositions are used comprising as the antifungal agent at least one member of the group: an azole, preferably miconazole, itraconazole, econazole, ketoconazole, fluconazole and a compound belonging to the group of polyenes such as natamycin and/or naftitin and comprising as the antibiotic at least one member of the group azithromycin, roxythromycin, clarithromycin, clindamycin, clyncomycin, thyrotricin, magainin, cecropine, natamycin, erythromycin and as a sulphonamide sulfadimidine and/or sulfamethoxazole.

Outstandingly suggested are those methods where synergistic compositions are used which comprise as active ingredients azithromycin : miconazole : sulfamethoxazole in the mass ratio 0,5 - 1,5 : 0,5 - 1,5 : 90 - 190 preferably about 1 : 1 : 140.

Further object of the invention are methods of treatment which represent the sub-group of the above method namely method to be used for human or veterinary

treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries of the living skin, external ulcers, burn injuries, necroses caused by irradiation, wounds to prevent or cure infections, to restore the epithelium by way of topically applying the combination

a) comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment

i) a fungicide, which is preferably azole or polyene type and

ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and

iii) a bacteriostatic sulphonamide,

iv) an active ingredient promoting circulation of the blood and body fluids preferably azulene or guaiazulene,

v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide

b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 whereby the ratio of the carrier is about 80 - 99 mass%.

According to a preferred method of treatment according to the above a synergistic drug comprising the following is applied: azithromycin 0,01 - 1,5 mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax. Azulene can be also used in the form of aetheroleum camomillae and/or aetheroleum millefolii.

Another subject of the invention as a sub-group of the above general treatments is the method for human or veterinary treatment of cavities of the body, the vagina,

the rectum and their epithelium and mucous membranes to prevent and cure injuries and infections caused by micro-organisms which are opportunally pathogens in these areas and which are often responsible for sexually transmitted diseases in humans and other mammals, comprising the local application of a combination or composition

a) comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment

i) a fungicide, which is preferably azole or polyene type and

ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and

iii) a bacteriostatic sulphonamide,

iv) an active ingredient promoting circulation of the blood and body fluids preferably azulene or guaiazulene,

v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide

b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 whereby the ratio of the carrier is about 80 - 99 mass%.

The composition used for the method of treatment comprises as a carrier at least one water-immiscible vegetable or mineral oil, fat and/or wax such as vaseline, lanalcol, cetyl stearate and/or beeswax. These contain each active ingredient suspended, emulgated or dissolved in the carrier.

Local administration is carried out preferably with ointments, effervescent tablets, sprays or foams in usual carriers. Sprays and foams may be used which comprise as addition carriers polysiloxane and/or oligosiloxane and optionally a power gas to ensure that the drug reaches the surface to be treated.

For the treatments the compositions have to be used in the following dose units: when ointments, sprays or

foams are used it is equally necessary for the layer on the treated surface to be of 10 - 15 mg/cm^2 strength. Using ointments however - specifically when gauze bandages are also applied - the applied total doses can be raised to 20 to 90 mg/cm^2. Usually one or two treatments per day are sufficient. At the beginning of the treatment or when large, open wounds with strong discharge are treated it is possible to administer the composition several times per day.

When performing the treatments according to the invention it is advisable to do the following:

The medicine (ointment, spray. foam) can be administered directly to fresh, not very sensitive wounds. In sensitive and strongly painful cases it is suitable to use the spray or the foam formulations or the ointment has to be applied on a gauze which is then covered over the wound. The bandage is changed every 12 or 24 hours. The wounds are epithelized from the edges to the centre and by way of filling in the wounds from the deeper sections upward in a spectacular manner and are healed without formation of crusts.

Burns which are already several days or weeks old or other slowly healing wounds covered with "armour-like" crusts are treated as follows: The whole surface to be treated is covered with the composition. It is suitable to use a spray or foam or to use the method of covering a gauze base, whereby the bandage should be changed every 12 or 24 hours. Depending on the thickness of the crust the composition effects already within 10 to 30 minutes reduction of pain and on entering into the hard crust softens the same and makes it flexible. On the course of later changes of the bandage the crust is detached in several pieces. However granulation starts already under the crust and in the following the wound is healed from the bottom in upward direction.

Treatment of cavities has to be practically accomplished to ensure the uniform layer containing the above indicated dose of 10 - 15 mg/cm^2 on the injured mucous membrane. This can be brought about by using suppositories of proper size. One or two treatments a day are recom-

mended. The treatment has to be repeated if the composition was washed or wiped away.

For the use of foams it is necessary to apply a head with a dosing nozzle where the quantity of the leaving material can be calibrated (preferably by the manufacturer).

Cavities can also be treated with one or two tablets a day which are entered into the cavity. Effervescent tablets are preferable. The tablet disintegrates within about 2 to 10 minutes and the combination exerts its activity on the injured or whole mucous membrane healing or preventing the ulcus-formation. The size of the tablet or suppository amounts preferably to 2 to 4 g.

The advantages of the pharmaceutical according to the invention are summarised in the following without the aim of completeness:

When treating skin wounds and ulcers strong local blood circulation starts already in the beginning, local pain reduction and disinfection takes place. No crust and scabs are formed. In case of great surface burns there is no need of surgery to eliminate the crust. A smooth surface is formed with a skin equal to the original in flexibility and quality. The use of the drug is simple, no need for previous disinfection. The dead tissues are detached.

It can also be used for treatment of sun burns, to accelerate local circulation, to treat scars.

The ingredients ensure that the formation of tissue and epithelium are in harmony and thus the basis of the skin develops attached to the basis of the wound and thus there is no scar line in the line of the wound and a smooth skin surface is achieved. As a consequence of painless healing there are no contractions, the joints and muscles are able to move freely during the full procedure.

In the case of first order burns the pain is soothed within some minutes also in cases of big burned surfaces; in second order burns pain is soothed within 15-20 minutes depending on size of the surface.

It is not necessary to peel the burnt surface. If blisters have to be treated it is sufficient to drain the fluid and cover the surface with the composition without eliminating the burnt tissues.

The surface of the skin heals practically without leaving a trace in cases of first and second grade burns. Third grade burns leave aesthetically acceptable results.

In the case of bed-sore (decubitus) appearing on the spots of pressure (where there is practically no circulation, the pain increases and the tissues are necrotized and then infected) the advantages of the composition are the above cited ones. The wounds on the pressure points of the back are healed though the patient is laying thereon.

The composition can be successfully used also in the treatment of bites - of course it does not replace protective vaccinations (e.g. against rabies). Infections are avoided, pain is soothed, quick regeneration of the tissues takes.

Use in and around the edges of cavities successfully heals the wounds in the area without infections in a similar manner.

In treatment amd prevention of sexually transmitted diseases and in the field of obstetrics and gynaecology the following diseases can be treated successfully: herpes genitalis, condyloma acuminatum (after laser treatment), episiotomy, secondary wound healing after episiotomy, epithelial lesions of the vulva etc.

The combination can be used for veterinary treatments. Animals to be treated include house animals, wild animals and pets as far as they are available for regular treatment. Economically important are cattle, horses, pigs, dogs, cats, monkeys, laboratory test animals, deer, wool and fur animals such as sheep, foxes etc. The wounds are closed within a short time followed by recovery of the animal. Full regeneration of the fur of the animals is practically complete in most cases.

The composition was used successfully in the treatment of wounds which apppeared specifically in the veterinary field as a consequence of the following diseases: abscessus, abscessus interdigitalis, fistulae, ulci, callus pyoderma, combustio, congelatio, decubitus, dehyscalated wounds, dermatitis of different types including D. interdigitalis, D. scroti, D. podo, D. allergica, excemas of different types, excoriatio, filum suppuratio, furunculos, hot spot, cheloids, lick granuloma, mastitis, shell inju-

ries (tortoise), perianalis fistula, perianalis necrosis, dermatitis pustula, pyoderma, skinfold pyoderma, plantar ulcer, plantar erosion, vulnus contusum, vulnus punctum etc.

The invention is illustrated in the following examples without the intention of limitation.

I. BIOLOGICAL EXAMPLES

The MIC value is the minimal concentration of the test material in the nutrient medium which inhibits proliferation of the chosen test organism at test conditions. When reducing concentration of the test material under the inhibiting concentration proliferation starts.

Test media:

For bacteria: Soya bouillon containing in the usual manner tripsine digested casein, soy peptone, glucose, sodium-chloride, potassium hydrogen phosphate and distilled water.

For fungi: Sabouraud nutrient liquid containing glucose, tripsine digested casein and water.

The experiments are carried out in an ambience free of germs.

To determine the MIC value an approximate concentration row was prepared from the samples in the nutrient liquor. Dissolution was made at 60 °C in a water bath. Composition of the concentration sequence:

- 100 µl of the different solutions of the samples
- nutrient liquid of stable volume (9,8 mL).

3-3 parallel samples of each member of the row were inoculated with 10 µl of the ready inoculum. The samples to be tested were dissolved in a solvent. As the negative control sample a nutrient medium without test material was used. The positive control was a nutrient medium + 100 µl of the inoculum + optionally a solvent.

Example I.1 - MIC values of active ingredients on 9 different microbe strains.

The following compounds were tested: azithromycin, clarithromycin, erythromycin, miconazole, primicin-sulphate. Test organisms: Bacteria: Escherichia coli, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus, Streprococcus pyogenes. Fungi: Aspergillus flavus, Fusarium oxysporum, Candida albicans, Candida parapsilosus. Nutrient media: Soye bouillon, Sabouraud nutrient liquor. Solvents: methanol a.r. and for primi-

cin-sulphate the mixture of butanol : ethanol : water in the ratio of 1 : 1 : 2. Negative control: nutrient medium exempt of test organisms. Positive control: nutrient medium and 10 µL of the inoculum.
Following preparation of the inoculum and incubation the MIC values were determined according to the above. The results are summarized in Table I.

Table I - MIC values (µg/ml)

active ingredient → microbe ↓	azithro-mycin	clarithro mycin	erythro-mycin	micon-azole	primycin
Escherichia coli	6,0	95	100	500<	100<
Staphylococcus aureus	2,0	0,2	1,0	3,0	0,2
Pseudomonas aerugi-nosa	65	80	90	500<	100<
Serratia marcescens	8,0	100	300	500<	100<
Streptococcus pyogenes	3,0	1,0	3,0	0,5	0,5
Aspergillus flavus	500<	100<	500<	2,0	100<
Fusarium oxysporum	500<	100<	500<	8,0<	100<
Candida albicans	500<	100<	500<	0,5	18
Candida parapsilosis	500	100<	500	0,2	5,0

Azithromycin is effective on all tested bacteria, including Escherichia coli. Proliferation of cocci is inhibited by all agents. Prymicin is acceptably active against Candida type fungi but not against all tested bacteria. Miconazole inhibits all tested fungi and cocci.

Example I.2. - Determination of MIC values on a Staphylococcus aureus strain of ointments containing different active ingredients.

Nine ointments were tested using the following marks: AMS, Ø, A, M, S, AM, AS, Msm AMS-P20, 28-alk (the meaning of the marks is indicated on Table I where the end results are summarized) and as test organism the strain Staphylococcus aureus ATCC 6538 obtained from DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH) was used. The compositions in the ointments were identical and corresponded to example II/1 with the difference that the active ingredients were those enlisted in Table II. The samples of ointments were dissolved in 1-butanol puriss.

The maximal concentration of the ointment which could be dissolved was 10 mg/ml. Positive control: nutrient medium + 100 µl of the inoculum + 100 µl 1% 1-butanol. MIC-value was the ointment concentration where no proliferation was observed in the correspondent solution. The results are summarized in Table II.

Table II

mark of ointment	*active ingredient*	*MIC (mg/ml)*
AMS	azithromycin + miconazole + sulfamethoxazole	2,0
Ø	-	>10,0
A	azithromycin	4,0
M	miconazole	>10,0
S	sulfamethoxazole	>10,0
AM	azithromycin + miconazole	3,0
AS	azithromycin + sulfamethoxazole	3,0
MS	miconazole + sulfamethoxazole	>10,0
AMS-P20,28-ALK	azithromycin + miconazole + sulfamethoxazole dissolved in paraffin-wax	2,0

The results show synergism on the tested microbe. Addition of both miconazole and sulfometoxazole increased the effect of azithromycin. The lowest MIC value was observed in the presence of all three active ingredients. The carrier did not decrease the activity.

General Method used in the following Examples I.3 to I.10:
Cylinder plate method (agar diffusion method): This biological method depends upon diffusion of the antibiotic from a vertical cylinder through a solidified agar layer in a Petri dish to an extent such that growth of the added microoganism is prevented entirely in a circular area or 'zone' around the cylinder containing the antibiotic preparation.
Test media:
For bacteria: - Müller-Hinton agar containing beef infusion; solids 4 g, acidic hydrolysate of casein 17.5g, starch 1.5 g, agar 17 g, 1000 ml distilled water;

-Tripticase-Soy agar containing pancreatic digest of casein 15 g, papaic digest of soybean 5 g, sodium chloride 5 g, agar 15 g, in 1000 ml distilled water.
For fungi:- Sabouraud-dextrose agar containing 40 g dextrose, 10 g peptone, 15 g agar, 1000 ml distilled water
- Tripticase-soy agar
The media were inoculated with 0.12-2 ml culture solutions diluted with physiological saline so that the germ number amounted to 10^4-10^6/ml in the agar layer.
Plastic Petri dishes (20 x 100 mm) were used for the assay and the agar layer was about 4 mm. Each sample was tested on 3 parallel inoculated Petri dishes.

Test organisms:	Staphylococcus aureus	ATCC 6534
	Streptococcus pyogenes	ATCC 19615
	Escherichia coli	ATCC 8739
	Klebsiella pneumoniae	CIP106976
	Clostridium perfringens	ATCC 9081
	Serratia marcescens	ATCC 43424
	Proteus mirabilis	ATCC 12453
	Candida albicans	ATCC 10231
	Aspergillus niger	ATCC 16404

Example I.3. - Inhibitory Effect of Ointments on Different Test Organisms (antimicrobial capacity or potency):
Test samples: Active ingredients tested in the ointment form according to Example II.2:
azithromycin, sulfamethoxazole, miconazole, azithromycin + sulfamethoxazole, azithromycin + miconazole, sulfamethoxazole + miconazole. The ointment without any antimicrobial compounds was used as blank sample.
The ointment samples were placed in a 7.5 mm diameter cylinder and incubated for 24 hours in case of bacteria and 48 hours in case of fungi at the appropriate temperature.
Results are shown in Table III:

TABLE III - Inhibition zone in mm

active → ingredient microbe ↓	b*	sulf	azit	mico	mico. + azit	azit.+ sulf.	mico. + sulfa-	azit+ mico+ sulfa.
Staphylococcus aureus	0	0	14.68	0	12.79	14.73	0	12.64
Streptococcus pyogenes	0	0	22.51	0	21.27	23.59	0	20.0
Proteus mirabilis	0	10.18	2.72	0	0	7.3	5.75	7.3
Escherichia coli	0	9.81	11.41	0	9.25	10.88	9.35	10.64
Klebsiella pneumoniae	0	10.46	10.27	0	5.65	12.95	7.73	10.56
Serratia marcescens	0	7.05	8.25	0	5.03	8.83	2.65	6.80
Clostridium perfringens	3.34	3.30	16.22	4.97	14.24	18.94	3.88	13.84
Candida albicans	0	0	0	10.01	9.94	0	8.94	10.02
Aspergillus niger	0	0	0	9.65	8.4	0	8.4	8.69

azit: azithromycin; sulf: sulfamethoxazole; mico: miconazole

Using azithromycin, sulfomethoxazole and miconazole together makes this ointment effective against all the tested bacteria and fungi strains. In case of Klebsiella pn., Serratia m. and Clostridium perf. synergism was found between azithromycin and sulfometoxazole increasing their activity mutually. The Gram positive bacillus Clostridium perf. seems to have susceptibility to some other component of the ointment, probably to the essential oils /Chamomillae and Achillea oils/.

Example I.4 - Antimicrobial Effect of the Vaginal Tablets
Tablets were prepared according to Example II.6. Antimicrobial capacity of tablets was tested with the cylinder plate method described in Example I.3, but the tablets were placed onto the surface of the agar layer not in a cylinder. Samples were incubated as described before. Results are shown in Table IV.

TABLE IV

Test organisms	Inhibition zone in mm
Staphylococcus aureus	14.8
Streptococcus pyogenes	20.2
Serratia marcescens	27.87
Clostridium perfringens	11.14
Candida albicans	19.13
Aspergillus fumigatus	22.21

The results show that the tablet form is effective against aerob, anaerob bacteria and fungi in vitro.

Example I.5. - Antimicrobial Effect of Spray Formulations The spray was prepared according to Example II.9. Microbiological tests were carried out with ointments and sprays parallel with the cylinder plate method as described in Example I.3. The sample was sprayed into a syringe and immediately thereafter the samples were placed into the cylinder. Results are shown in Table V:

TABLE V - Inhibition zone in mm

Test organisms	Spray	Ointment
Staphylococcus aureus	18.13	11.83
Streptococcus pyogenes	31.38	23.25
Serratia marcescens	12.64	4.75
Clostridium perfringens	16.63	3.07
Aspergillus fumigatus	11.3	4.08

The above show good effects for both formulations. Spray samples have larger inhibition zones than the ointments probably as a consequence of their carrier, hexamethyldisiloxane, promoting diffusion of the active ingredients.

Example I.6 - Antimicrobial Efficacy of Erythromycin Combinations in the Ointment Form.

Test samples: The following active ingredients were tested in the ointment form described in Example II.1:

erythromycin, sulfamethoxazole, miconazole, erythromycin + sulfamethoxazole, erythromycin + miconazole, erythromycin + sulfamethoxazole + miconazole. The ointment without any antimicrobial compounds was used as blank sample.
Ointments were prepared according to Examples II.3. The antimicrobial effectiveness of these preparation was tested with the cylinder plate method as described in Example I.3. Results are shown in Table VI:

TABLE VI

active ingredients → microbes ↓	sulfa	eryth	mico	eryth. + sulfa	eryth.+ mico	eryth + mico+ sulfa
Staphylococcus aureus	0	19.76	0	19.18	19.84	19.51
Serratia marcescens	5.67	5.33	0	7.28	6.25	6.12
Clostridium perfringens	0	17.93	3.47	17.24	19.23	16.89
Candida albicans	0	0	8.73	0	12.70	12.12

erit: erythromycin; sulf: sulfamethoxazole; mico: miconazole

It follows from the above that the ointments show a strong antibacterial and antifungal capacity. A clear synergistic effect was found between erythromycin and miconazole.

Example I.7 - Antimicrobial Effect of Ointments
Ointments were prepared according to Examples II.2 where Azithromycin was substituted with Clarythromycin and tested as described in Example I.3.
Test samples: The following active ingredients were tested in the ointment form described in Example II.1:
clarithromycin, sulfamethoxazole, miconazole, clarithromycin + sulfamethoxazole, clarithromycin + miconazole, clarithromycin + sulfamethoxazole + miconazole. The ointment without any antimicrobial compounds was used as blank sample. Results are shown in Table VII.

TABLE VII

Active ingredients → microbes ↓	sulfa	clarit	mico	clarit. + sulfa	clarit.+ mico	clarit+ mico+ sulfa
Staphylococcus aureus	0	17.51	0	17.48	18.24	14.02
Streptococcus pyogenes	5.4	2.1	0	4.85	2.41	5.25
Clostridium perfringens	0	18.83	2.69	19.49	19.56	13.74
Candida albicans	0	0	8.44	0	12.48	12.12

clarit: clarithromycin; sulf: sulfamethoxazole; mico: miconazole

It follows from the above that the ointments show a strong antibacterial and antifungal capacity. A clear synergistic effect was found between clarithromycin and miconazole.

Example I.8

Comparative Antimicrobial Test of Suppositories for Rectal Administration and Ointments

Suppositories were prepared according to Examples II.7. Microbiological testing was carried out with cylinder plate method as described in Example I.3. The suppository samples were resembled to the ointment samples on the same Petri dish. Suppositories were cut into cylinders 4 mm height and 7 mm in diameter and put into the wells of the agar layer. At the incubation temperature - 37C°- suppositories melted and active ingredients could diffuse into the agar layer. Results are shown in table VIII:

TABLE VIII - Inhibition zone in mm

Test organisms	Suppository	Ointment
Staphylococcus aureus	18.26	10.67
Streptococcus pyogenes	31.91	21.31
Clostridium perfringens	20.61	16.63
Candida albicans	6.86	7.47
Aspergillus fumigatus	23.72	4.08

It follows from the above that both formulations effectively inhibit aerob and anaerob bacteria as well as fungi. The larger inhibition zone of suppository samples were assigned to its carriers and the fact that the preparation becomes liquid at 37 C° which supports diffusion of the active ingredients.

Example I.9

Antimicrobial Efficacy of Ointments.

Ointments were prepared according to examples II.11, II.12 using the polyene type antifungal nystatin instead of miconazole. The antibacterial and antifungal capacity of preparations were tested with the cylinder plate method as described in example I.3.

Test organims:

Staphylococcus aureus
Streptococcus pyogenes
Clostridium perfringens
Candida albicans
Aspergillus fumigatus

It follows from the results that the ointments show marked antimicrobial effects against both fungi and bacteria.

Example I.10

Antimicrobial Efficacy of Ointments.

Ointments were prepared according to examples II.11, II.12 using the polyene type antifungal naftitin instead of miconazole. The antibacterial and antifungal capacity of preparations were tested with the cylinder plate method as described in example I.3.

Test organisms:

Staphylococcus aureus
Streptococcus pyogenes
Clostridium perfringens
Candida albicans
Aspergillus fumigatus

It follows from the results that the ointments show marked antimicrobial effects against both fungi and bacteria.

II. COMPOSITIONS

Example II.1 - Ointment

Composition:

	mass %	g
azithromycin	0,020	0,1
miconazole	0,020	0,1
sulfamethoxazole	2,80	14,0
ZnO	3,75	18,75
cetyl stearate	1,25	6,25
lanalcol	3,37	16,85
cera alba	3,11	15,55
vaseline ophth.	20,90	104,5
aetheroleum chamomillae	0,56	2,80
aetheroleum millefolii	0,56	2,80
vaseline (white)		ad 500

The above composition ensures the 10^2-fold concentration of the MIC values evaluated on cultures of microbes which we estimated to be of key importance (Tests I.1 and I.2). It can be used as an ointment.

General method to prepare the ointments:

The zinc oxide and sulphonamide are measured into a mortar and are homogenised thoroughly, whereupon the powder mixture is transferred into a vessel measured complete with the stirrer. The needed amounts of cetyl stearate, lanalcole, cera alba, vaseline, paraffin-wax components are added into an other vessel and this mixture is melted. The melt is added in portions to the powder mixture under continuous stirring and cooling with ice water. Azithromycin and miconazole are dissolved in absolute ethanol and the amounts of aetheroleum chamomillae and aetheroleum millefolii are added thereto. The blue solution thus obtained is stirred into the cold ointment. The originally white ointment is stirred until homogeneously blue. Thereupon the desired amount of paraffin-wax is homogeneously admixed. A blue ointment is obtained which is ready to use. The stable shelf life in closed tubes under normal conditions amounts to a least 2 years.

Example II.2 - Ointment

Composition:

	mass%	g
clarithromycin	0,040	0,2
miconazole	0,020	0,2
sulfamethoxazole	2,80	14,0
ZnO	3,75	18,75
cetyl stearate	1,25	6,25
Lanalcol	3,37	16,85
Cera alba	3,11	15,55
Vaseline ophth.	20,90	104,5
camomile	0,56	2,80
millefolii	0,56	2,80
vaseline (white)		ad 500,00

Preparation: See Example II.1.

Example II.3 - Ointment

Composition:

	mass%	g
erythromycin	0,10	0,5
miconazole	0,020	0,1
sulfamethoxazole	2,80	14,0
ZnO	3,75	18,75
cetyl stearate	1,25	6,25
lanalcol	3,37	16,85
cera alba	3,11	15,55
vaseline ophth.	20,90	104,5
aetheroleum chamomillae	0,56	2,80
aetheroleum millefolii	0,56	2,80
vaseline (white)		ad 500

Preparation: See Example II.1.

Example II.4 - Ointment

Composition:

	mass%	g
azithromycin	0,02	0,1
miconazole	0,02	0,1
sulfamethoxazole	2,80	14,0
ZnO	3,75	18,75
cetyl stearate	1,25	6,25
lanalcol	3,37	16,85
cera alba	3,11	15,55
vaseline ophth.	20,90	104,5
aetheroleum chamomillae	0,56	2,80
aetheroleum millefolii	0,56	2,80
vaseline (white)		216,92
paraffin-wax liquidum		101,38

Preparation: See Example II.1.

Example II.5 - Ointment for Veterinary Use

Composition:

	mass%	g
erythromycin	0,1	0,5
miconazole	0,02	0,1
sulfamethoxazole	2,80	14,0
ZnO	3,75	18,75
cetyl stearate	1,25	6,25
lanalcol	3,37	16,85
cera alba	3,11	15,55
vaseline ophth.	20,90	104,5
aetheroleum chamomillae	0,56	2,80
aetheroleum millefolii	0,56	2,80
vaseline, white		216,52
paraffin-wax, liquid		101,38

Preparation: See Example II.1.

Example II.6 - Ointment

Composition:

	mass %	g
azithromycin	0,020	0,1
nystatin	3,0	15,0
sulfamethoxazole	2,80	14,0
ZnO	3,75	18,75
cetyl stearate	1,25	6,25
lanalcol	3,37	16,85
cera alba	3,11	15,55
vaseline ophth.	20,90	104,5
aetheroleum chamomillae	0,56	2,80
aetheroleum millefolii	0,56	2,80
vaseline (white)		ad 500

Preparation: See Example II.

Example II.7 - Ointment

Composition:

	mass %	g
azithromycin	0,020	0,1
naftitin	1,0	5,00
sulfamethoxazole	2,80	14,0
ZnO	3,75	18,75
cetyl stearate	1,25	6,25
lanalcol	3,37	16,85
cera alba	3,11	15,55
vaseline ophth.	20,90	104,5
aetheroleum chamomillae	0,56	2,80
aetheroleum millefolii	0,56	2,80
vaseline (white)		ad 500

Preparation: See Example II.

Example II.8 Tablet for Vaginal Administration

Composition:

	1 tablet g	1 batch g
azithromycin	0,35	1,05
miconazole	0,35	1,05
sulfamethoxazole	47,60	142,80
lactose	914,00	2742,0
Vivapur® 102 (Merck)	220,00	660,0
adipic acid	110,00	330,0
$NaHCO_3$	88,00	264,0
Mg-stearate	16,00	48,0
Aerosil	3,70	11,1
Total	1400	4200

The following mixtures are prepared first:

a) Miconazole and azulene are mixed in a mortar with sulfamethoxazole which is added in portions followed by the other ingredients.

300 g lactose are added while mixing followed by sieving through a 0,630 mm sieve.

b) Aerosil 20 is mixed with 100 g lactose and the mixture is sieved through a 0,630 mm sieve.

c) Sodium-hydrogen-carbonate and adipic acid are pulverized and mixed together, followed by sieving through a 0,200 mm sieve.

d) Mg stearate is sieved through a 0,200 mm sieve.

The mixtures a+b+c are mixed and homogenized. Finally Mg-stearate is added and homogenized. Tablets are then prepared substantially in the usual manner.

Example II.9 Tablet for Vaginal Administration
Composition:

	mass%
azithromycin	0,02
miconazole	0,02
sulfamethoxazole	2,80
stearine	0,5
aerosil 2000	0,25
TWIN 20	0,12
magnesium stearate	1,2
sodium hydrogen carbonate	6,47
adipic acid	8,39
maize starch	10,6
lactose	69,73

Tablets are prepared from the above in the usual manner. The tablets disintegrate in the vagina within 10 minutes.

Example II.10 - Suppositories for Rectal Administration
Composition:

	mass%	g
azithromycin	0,02	0,06
miconazole	0,02	0,06
sulfamethoxazole	2,8	8,4
adeps solidus		ad 300

Preparation: 100 pieces of 300 mg suppositories are prepared from the above in the usual manner.

Example II.11 - Suppositories for Vaginal Administration
Composition:

	mass%	g
azithromycin	0,02	0,06
miconazole	0,02	0,06
sulfamethoxazole	2,8	8,4
butyrum cacao		ad 300

Preparation: 100 pieces of 300 mg suppositories are prepared from the above in the usual manner.

Example II.12 - Suppository for Rectal or Vaginal Administration

Composition:

	mass%	g
azithromycin	0,02	0,2
miconazole	0,020	0,2
sulfamethoxazole	2,80	14,0
ZnO	3,75	18,75
aetheroleum chamomillae	0,56	2,80
aetheroleum millefolii	0,56	2,80
Witepsol® (Hüls)		ad 500,00

Preparation: See Example II.9.

Example II.13 - Spray

Composition:

	g
azithromycin	0,1
miconazole	0,1
sulfamethoxazole	14,0
zinc oxide	18,75
cetyl-stearate	6,25
lanalcol	16,85
cera alba	15,55
vaseline (white) ophth.	104,4
vaseline (white)	318,3
aetheroleum chamomillae	2,80
aetheroleum millefolii	2,80
DM 0.65 hexamethyldisiloxane	500,00

Preparation: An ointment is prepared from the correspondent ingredients according to Example II.1. This product is dissolved cold (10 - 15 °C) in DM 0.65 hexamethyldisiloxane (Wacker-Chemie GmbH.) carefully because the danger of fire. The product is filled into flasks taking into account that the specific volume is large so that about the flasks can be filled to about the half. It can be sprayed with an air pump onto the surface to be treated to form a uniform oily layer.

Example II.14 Foam

Composition:

	t%
ointment according to Example II.1	48
DM 0.65 hexamethyldisiloxan	2
DM 100 polydimethylsiloxan	50

Preparation: An ointment is prepared according to Example II.1 using the same ingredients which is dissolved cold (10 - 15 °C) in DM 0.65 hexamethyldisiloxan® whereupon DM 100 polydimethylsiloxan® (Wacker-Chemie GmbH.) is added. A suspension is formed which is filled into flasks along with an inert power gas; filling ratio: 75 mass% gas, 25 mass% composition. Applied on the treated surface a foam appears which collapses to form a uniform oily layer well covering the surface for 24 hours.

III. IN VIVO TREATMENTS

Example I.3. Treatment of a burn wound.

C.J. 30 years old male patient suffered II order burns on an about 900 cm^2 of the right crural surface caused by a paint-diluting solvent which was spilled on his trousers and inflamed. He was painted at the traumatology with Merbromin® (active ingredient mercurochrom). After 1 week a thick crust was formed, he had severe pain; plastic surgery was planned. We started regular once a day treatment of this wound covered by a crust of about 4 - 8 mm thickness with the blue ointment prepared according to Example II.1. The crust became detached on the first day, the surface underneath was inflamed, stenchy with strong discharge. The pain ceased on the course of the first day. Starting from the 6th day formation of a new skin was observed on the contour of the wound. On the 8th day the surface with discharge was reduced to two 1 cm x 4-6 cm stripes. There was no open wound on the 9th day. The patient left driving his own car on a 460 km route without pain and fatigue. The wound was finally cured without scars.

Example III.2 - Early clinical results on human patients. Treatments were carried out on an outpatient base with the

preparation according to Example II/6. The ointment was applied topically, in the beginning daily as needed at least once or twice or more when a strong discharge of exudate was present. Wounds without an exudate were not or no longer covered with gauze.

K.CS. male, 4 years old, diagnosed with third degree burn wound on the right side of the left foot, with the size of about 2x3 cm. He was treated with the preparation and the wound completely healed within 11 days.

F.A. male, 31 years old, two years ago diagnosed with varicoses, now has dermatosclerosis on the right lower limb having four ulcera (one of them about 2.5 x 1 cm size) on the middle of the sclerotic area. He was treated with the preparation and the ulcera were closed, the wounds healed after seven weeks.

M.J., female, 66 years old, diagnosed with diabetes, hypertonia and varicosis on the left lower limb, with a strong discharge of exudate from a 3x4 cm ulcer. She was treated with the preparation and the ulcer was closed and the wound healed after nine weeks (see photocopies on Figure 1 A and B).

D.J., female, 50 years old, diagnosed with trombophlebitis since 25 years, introduced to the treatment for an ulcer on the right lower limb, just over the ankle on the inner site. She was treated with the preparation and the ulcer was closed and the wound healed after four weeks.

M.K., male, 68 years old, diagnosed with varicoses, has a 3x6 cm ulcer on the left lower limb persistent since two months. He was treated with the preparation and the ulcer was closed and the wound healed after 11 weeks (see photocopies on Figure 1 C and D).

S.O., female, 77 years old, diagnosed with varicoses, has a 1x1 cm, deep ulcer on the left lower limb just over the ankle. She was treated with the preparation and the ulcer was closed and the wound healed after ten weeks.

EXAMPLE III/3 - Veterinary Treatments
In the following treatment of seven different types of animals are demonstrated using the concrete example of one or two animals for each group. All cases were reported by the Veterinary Clinic of Budapest. Wounds and injuries were treated with the ointment prepared according to Example II.6. Improvement was measured by veterinarians.

a) Horse, 3 years old Hungarian half-bred mare, weight: 350 kg. Case history: 11.04.2002 burn and torn wound on limb. Treatment: topical twice daily, no bandage. 20.04.2002 wound healing.
b) Guinea-pig, 2 years, female, weight: 50 gr. Case history: 14.03.2002 bitten by a dog. Treatment: topical, once daily. 24.03.2002 wound closed, recovered.
c) Tortoise, 13 years, male, weight: 500 g. Case history: 11.03.2002 bitten by a dog, shell broken, injured soft tissue. Treatment: topical, twice daily of the wound. 12.04.2002 wound closed, distinct improvement.
d) Dog, 13 years, male, middle Poodle, weight: 7 kg. Case history: 23.01.2001 burn wound. Treatment: twice daily topical 02.02.2002 recovered.
e) Dog, 3 years, male, West Highland White Terrier, weight: 10 kg. Case history: 25.01.2001 scald on its chest, first grade burn wound. Treatment: once daily, topically. 11.04.2001 wound healed, full recovery.

Example III.3: - Treatment of sexually transmitted diseases in human patients.
Tablets according to Example II.8 were used in the following 3 groups of women suffering from bacterialis vaginosis (15 cases) of vulvovaginalis candidiasis (21 cases) and Trichomonas vaginitis (6 cases) respectively. All women were in the fertile age and were more or less infected by all three types of microbes. The three groups were named on the basis of the dominant vaginal infection observed by way of the following means: anamnesis, physical investigation,

pH of the vaginal fluid, potassium-hydroxide test, microscopic investigation of a smear taken from vaginal fluid. Treatment: After the evening bath 1 tablet was placed into the vagina for 3 consecutive days. Vaginal pH was determined before and after treatment. The results of 42 patients treated within a period of 3 months are summarized below in TableS IX, X and XI respectively; average pH values are indicated.

TABLE IX

Vaginosis Bacterialis(15 cases)

	Vaginal pH	Subjective complaints	KOH-test
before treatment	5,5	pungent odour fluid	positive
after treatment	4,5	normal fluid	negative

results:	improved	no change	worse
	11	4	-

TABLE X

Candidiasis Vulvovaginalis(21 cases)

	vaginal pH	subjective complaints	fungus lines in native cytology
before treatment	4,8	curdled fluid	positive
after treatment	4,5	normal fluid	negative

	improved	unchanged	worse
results:	18	3	–

TABLE XI

Vaginitis Trichomonalis (6 cases)

	Vaginal pH	Subjective complaints	KOH-test
before treatment	5,0	pungent odour foamy fluid	positive
after treatment	4,5	normal fluid	negative

results:	improved	no change	worse
	11	4	–

It is clear for the expert that most of these treatments were carried out in combination with internal medication. In cases of Vaginitis Trichomonalis the treatment was com-

pleted with both oral Klion therapy and treatment of the sexual partner.
Summarizing the results it can be stated that use of the tablet is a promising alternative for the treatment of all three clinical cases isolated or (as it happens in most practical cases) in combination.

Example III.5 Use of the Ointment in Obstretics and Gynaecology
The ointment of Example II.6 was used in gyneaecological treatment of various wounds on a total of 80 patients suffering from the diseases enslited in Table X:

TABLE X

	Herpes genitalis	Condyloma acuminatum (after laser tr.)	Episiotomy	Secondary wound healing	Epithelial lesion on the vulva
cases	5	15	35	4	21

Treatment: Both sides of a gauze piece are smeared with the ointment and the gauze is placed into the wound or on the top of its surface. The gauze is changed once or twice a day. The wounds were generally closed within 2 to 3 weeks. Recovery within 4 to 16 weeks.

Claims

1. Medical combination preferably in one single composition against microbes which are pathogenic in humans and animals and which appear together or which represent a danger to appear together, said composition to be used for human or veterinary treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries or to be used in body cavities to prevent or cure infections,
   a) said composition comprising active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment of the following group
      i) at least one fungicide, which is preferably azole or polyene type and
      ii) at least one antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and
      iii) at least one bacteriostatic sulphonamide,
   b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment
   c) and where the mass ratio of said active ingredients amounts to i : ii : iii = 0,1 - 10 : 0,1 - 10 : 10 - 200 whereby the ratio of the carrier amounts to about 80 - 99 mass%.

2. Composition according to claim 1 comprising an antifungal ingredient which is effective against several human or veterinary pathogen strains of fungi belonging to the group Candida, Aspergillus, and/or Fusarium.

3. Composition according to any of claims 1 to 2 comprising an antifungal ingredient which is effective against pathogen strains of the following fungi: Candida tropicalis, Candida parapsilosis, Candida albicans, Torulopsis (Cand.) glabrata, Fusarium oxysporum,

Trishosporon beigelii, Aspergillus flavus, Aspergillus fumigatus, Aspergillis terreus, Aspergillus niger, Mucor spp, Rhizopus spp, and/or Penicilium spp.

4. Composition according to claim 3 comprising as the antifungal agent at least one member of the group: an azole preferably miconazole, itraconazole, econazole, ketoconazole, fluconazole and a compound belonging to the group of polyenes such as natamycin, nystatin, and/or naftitin.

5. Composition according to any of claims 1 to 4 comprising an antibiotic which is effective against preferably several members of the opportunally pathogenic strains of the following bacteria:
aerobic bacteria: Gram-negative bacilli such as Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus; Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species, Mycobacterium species such as Mycobacterium ulcerans, and/or microbes similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

6. Composition according to claim 5 comprising as an antibiotic at least one of the following: azithromycin, roxythromycin, clarithromycin, clyndamycin, clyncomycin, thyrotricin, magainin, cecropine, natamicin, eryhromycin.

7. Composition according to any of claims 1 to 6 comprising as a sulphonamide sulfadimidine and/or sulfamethoxazole.

8. Synergistic composition according to any of claims 1 to 7 comprising as active ingredient miconazole, azithromycin and sulfamethoxazole in the mass ratio of 0,1 - 1 : 0,1 - 1 : 10 - 35, preferably 0,1 : 0,1 : 14.

9. Composition according to any of claims 1 to 7 comprising as a carrier at least one water-immiscible vegetable or mineral oil, fat and/or wax.

10. Composition according to claim 9 comprising as a carrier vaseline, lanalcol, cetyl stearate, beeswax.

11. Composition according to any of claims 9 and 10 comprising each active ingredient suspended, emulgated or dissolved in the carrier.

12. Combination and composition according to any of claims 1 to 11 to be used for human or veterinary treatment of the skin epithelial lesions, epithelial deficiency, epithelial injuries of the living skin, external ulcers, burn injuries, necroses caused by irradiation, wounds to prevent or cure infections, to restore the epithelium
    a) said composition comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment
        i) a fungicide, which is preferably azole or polyene type and
        ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and
        iii) a bacteriostatic sulphonamide,
        iv) an active ingredient promoting circulation of the blood and body fluids , preferably azulene or guaiazulene,
        v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide

b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 the ratio of the carrier being about 80 - 99 mass%.

13. Synergistic composition according to claim 12 comprising the following: azithromycin 0,01 - 1,5 mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% preferably in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax.

14. Combination and composition according to any of claims 1 to 11 to be used for human or veterinary treatment of cavities of the body, the vagina, the rectum or their epithelium, mucous membranes, to prevent or cure infections, to restore the epithelium

a) said composition comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment

i) a fungicide, which is preferably azole or polyene type and

ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and

iii) a bacteriostatic sulphonamide,

iv) an active ingredient promoting circulation of the blood and body fluids, preferably azulene or guaiazulene,

v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide

b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 the ratio of the carrier being about 80 - 99 mass%.

15. Synergistic composition according to claim 14 comprising the following: azithromycin 0,01 - 1,5 mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% optionally in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax.

16. Composition according to any of claims 13 to 15 in the form of a suppository comprising as a carrier adeps solidus 50 and/or a triglyceride.

17. Composition according to any of claims 1 to 16 comprising as a further additive a pharmaceutically acceptable colouring agent, a perfume, a volatile oil.

18. Composition according to any of claims 1 to 17 which is formulated and packaged in the usual manner as an ointment, foam or spray and into the usual dosage forms and units suitable for such administrations.

19. Composition according to claim 18 formulated into spray or foam comprising as the carrier a polysiloxane and/or oligosiloxane and optionally a carrier gas to ensure that the composition reaches the surface to be treated.

20. Composition according to any of claims 14 to 19 for the treatment of body cavities formulated and packaged in the usual manner as a tablet, granule, suppository, foam, oily suspension, spray and comprising optionally

further correspondent auxiliary materials.

21. Method of treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries or to be used in body cavities to prevent or cure infections in humans or animals against such microbes which are pathogenic in humans or animals and which appear together or which represent a danger to appear together **comprising** the local application of a combination comprising at least one active ingredient which is effective against several of the fungal and bacterial strains (opportunally pathogenic on humans and animals) of the group consisting of *fungi* Candida, Aspergillus, and/or Fusarium, and aerobic *bacteria*: Gram-negative bacilli such as Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus, Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species and Mycobacterium species such as Mycobacterium ulcerans, *microbes* similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

22. Method of treatment according to claim 21 ***comprising*** the application of a combination comprising at least one active ingredient which is effective against several of the opportunally pathogenic microbes: Candida tropicalis, Candida parapsilosis, Candida albicans, Torulopsis (Cand.) glabrata, Fusarium oxysporum, Trishosporon beigelii, Aspergillus flavus, Aspergillus fumigatus, Aspergillis terreus, Aspergillus niger, Mucor spp, Rhizopus spp, and/or Penicilium spp.

23. Method of treatment according to claim 21 ***comprising*** the application of a combination comprising at least

one active ingredient which is effective against several of the opportunally pathogenic microbes: Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Enterobacter aerogenes, Enterobacter faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Citrobacter spp, Aeromonas spp,: Neisseria meningitidis, Acinetobacter anitratus, Corynebacterium spp, Bacillus sphaericus, Group D Streptococcus, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus faecalis, Streptococcus spp, Bacteroides fragilis, Bacteroides ovatus, Bacteroides spp, Fusobacterium mortiferum, Fusobacterium mucleatum, Peptococcus magnus, Peptococcus assaccharoliticus, Peptostreptococcus anaerobius, Peptostreptococcus micros, Clostridium welchii, Clostridium perfingens, Clostridium spp, Propionibacterium acnes, Eubacterium lentum, microbes similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

24. Method according to claim 21 comprising application of a synergistic combination preferably in one single composition
    a) said combination comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment
        i) a fungicide which is preferably azole or polyene type and
        ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and
        iii) a bacteriostatic sulphonamide,
    b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment
    c) and where the mass ratio of said active ingredients amounts to i : ii : iii = 0,1 - 10 : 0,1 - 10 : 10 - 200, the ratio of the carrier being

about 80 - 99 mass%.

25. Method of treatment according to any of claims 21 to 24 ***comprising*** the application of a combination comprising as the antifungal agent at least one member of the group: an azole preferably miconazole, itraconazole, econazole, ketoconazole, fluconazole and a compound belonging to the group of polyenes such as natamycin, nystatine and naftitin.

26. Method of treatment according to any of claims 21 to 25 ***comprising*** the use of a combination comprising as an antibiotic at least one of the following: azithromycin, roxythromycin, clarithromycin, clyndamycin, clyncomycin, thyrotricin, magainin, cecropine, erythromycin.

27. Method of treatment according to any of claims 21 to 26 ***comprising*** the use of a combination comprising as a sulphonamide sulfadimidine and/or sulfamethoxazole.

28. Method of treatment according to any of claims 21 to 27 ***comprising*** the use of a synergistic combination comprising as the active ingredients miconazole, azithromycin and sulfamethoxazole in the mass ratio of 0,1 - 1 : 0,1 - 1 : 15 - 35 preferably in the mass ratio 0,1 : 0,1 : 14.

29. Method of treatment according to any of claims 21 to 22 ***comprising*** the application of a combination or composition to be used for human or veterinary treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries of the living skin, external ulcers, burn injuries, necroses caused by irradiation, wounds (in the following "wounds") to prevent or cure infections, to restore the epithelium
    a) said composition comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment

i) a fungicide, which is preferably azole or polyene type and
ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and
iii) a bacteriostatic sulphonamide,
iv) an active ingredient promoting circulation of the blood and body fluids preferably azulene or guaiazulene,
v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide

b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 whereby the ratio of the carrier is about 80 - 99 mass%.

30. Method of treatment according to claim 29 ***comprising*** the application of a synergistic combination comprising the following: azithromycin 0,01 - 1,5 mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% optionally in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax and optionally polysiloxane, oligosiloxane and a carrier gas.

31. Method of treatment according to claim 29 comprising the use of a composition in the form of an ointment, spray or foam.

32. Method of treatment according to any of claims 21 to 28 for human or veterinary treatment of cavities of the body, the vagina, the rectum and their epithelium

and mucous membranes to prevent or cure infections and injuries ***comprising*** the local application of a synergistic composition

a) comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human or veterinary treatment
   i) a fungicide, which is preferably azole or polyene type and
   ii) an antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and
   iii) a bacteriostatic sulphonamide,
   iv) an active ingredient promoting circulation of the blood and body fluids , preferably azulene or guaiazulene,
   v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide
b) and where said active ingredients are dispersed in a carrier which is pharmaceutically acceptable on the site of treatment
c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 whereby the ratio of the carrier is about 80 - 99 mass%.

33. Method of treatment according to claim 32 comprising local use of the following combination in the form of a tablet, effervescent tablet, suppository, ointment or foam: azithromycin 0,01 - 1,5 mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% preferably in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax.

34. Method of treatment according to claim 33 comprising the use of a composition in the form of a suppository comprising as a carrier adeps solidus 50 and/or a triglyceride.

35. Method of treatment according to any of claims 21 to 34 in veterinary use.

Fig.A. Before treatment

Fig.B. After 9 weeks

Fig. C. Before treatment

Fig.D. After 11 weeks

INTERNATIONAL SEARCH REPORT

Ir. tional Application No
PCT/HU 02/00115

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7048 A61K31/4174 A61K31/137 A61K31/635 A61P17/02
A61P31/10 A61P31/02 A61P31/04 A61P15/02
//(A61K31/7048,31:635,31:4174,31:137)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EMBASE, EPO-Internal, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 03135 A (MILANKOVITS MARTON) 8 February 1996 (1996-02-08) page 2, line 16; claims 1-3 page 3, line 19 -page 4, line 19 page 8, line 10 -page 9 ---	1-11,17, 18,21-28
A	EP 0 125 759 A (UNILEVER PLC ;UNILEVER NV (NL)) 21 November 1984 (1984-11-21) claims 1-3; example 1 -----	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2003	06/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ansaldo, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 02/00115

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9603135 A	08-02-1996	HU 215443 B1	28-04-1999
		AU 2935095 A	22-02-1996
		EP 0772445 A1	14-05-1997
		WO 9603135 A1	08-02-1996
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		AT 67662 T	15-10-1991
		DE 3485100 D1	31-10-1991
		EP 0125759 A2	21-11-1984

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Published:
— *with international search report*
— *with amended claims and statement*

Date of publication of the amended claims and statement:
12 September 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMBINATONS COMPRISING A FUNGICIDE, A BACTERIOSTATIC SULPHONAMIDE AND AN ANTIBACTERIAL COMPOUND FOR TOPICAL APPLICATION

(57) Abstract: Medical combination and its method of topical use comprising active ingredients which are sparingly soluble in water, preferably in one single composition against microbes which are pathogenic in humans and animals and which usually appear together. It comprises at least one active ingredient which is effective against several of the opportunally pathogenic strains of the group consisting of *fungi* Candida, Aspergillus, and/or Fusarium, and aerobic *bacteria*: Gram-negative bacilli such as Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus, Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species and Mycobacterium species such as Mycobacterium ulcerans, *microbes* similar to bacteria of the Chlamydia species such as Chlamydia trachomatis. To be used for treatment of the skin or mucous membranes bearing epithelial lesions, deficiency or injuries and to be used in body cavities to prevent or cure infections and deficiencies. The composition contains - dispersed in a carrier which is pharmaceutically acceptable on the site of treatment - at least one fungicide, which is preferably azole or polyene type and at least one antibacterial compound preferably of the erythromycin, azalide, linkozamide, polypeptide type and at least one bacteriostatic sulphonamide. Additionals mainly for use on skin may include zinc oxide and asulene. Useful in forms of ointment, tablet, effervescent tablet, suppository, foam.

WO 03/039559 A1

[Received by the International Bureau on 06 May 2003 (06.05.03); original claims 1-35 replaced by new claims 1-53 (16 pages)]

1. Medical combination preferably in one single composition against microbes which are pathogenic in humans and animals and which appear together or which represent a danger to appear together,
containing active ingredients and carriers acceptable for human and veterinary treatment
   a) comprising only such active ingredients or such form of active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are as follows:
      i) at least one fungicide, which is preferably azole type and
      ii) at least one antibacterial compound preferably of the azalide, linkozamide, polypeptide or erythromycin-derivative type and
      iii) at least one sparingly water-soluble bacteriostatic sulphonamide,
   b) and where said active ingredients are dispersed in a water-free carrier which is pharmaceutically acceptable on the site of treatment
   c) and where the mass ratio of said active ingredients amounts to i : ii : iii = 0,1 - 10 : 0,1 - 10 : 10 - 200 whereby the ratio of the carrier amounts to about 80 - 99 mass%

   for human and veterinary treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries thereby preventing or curing infections.

2. Composition according to claim 1 comprising an antifungal ingredient which is effective against several human or veterinary pathogen strains of fungi belonging to the group Candida, Aspergillus and/or Fusarium.

3. Composition according to any of claims 1 or 2 comprising an antifungal ingredient which is effective against pathogen strains of the following fungi: Candida tropicalis, Candida parapsilosis, Candida albi-

cans, Torulopsis (Cand.) glabrata, Fusarium oxysporum, Trishosporon beigelii, Aspergillus flavus, Aspergillus fumigatus, Aspergillis terreus, Aspergillus niger, Mucor spp, Rhizopus spp, and/or Penicilium spp.

4. Composition according to claim 3 comprising as the antifungal agent at least one azole of the group miconazole, itraconazole, econazole, ketoconazole, fluconazole.

5. Composition according to any of claims 1 to 4 comprising an antibiotic which is effective against preferably several members of the opportunally pathogenic strains of the following bacteria:
aerobic bacteria: Gram-negative bacilli such as Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus; Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species, Mycobacterium species such as Mycobacterium ulcerans, and/or microbes similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

6. Composition according to claim 5 comprising as an antibiotic at least one of the following: azithromycin, roxythromycin, clarithromycin, clyndamycin, clyncomycin, thyrotricin, magainin, cecropine.

7. Composition according to any of claims 1 to 6 comprising as a sulphonamide sulfamethoxazole.

8. Synergistic composition according to any of claims 1 to 7 comprising as active ingredient miconazole, azithromycin and sulfamethoxazole in the mass ratio of

0,1 - 1 : 0,1 - 1 : 10 - 35, preferably 0,1 : 0,1 : 14.

9. Composition according to any of claims 1 to 7 comprising as a carrier at least one water-immiscible vegetable or mineral oil, fat and/or wax.

10. Composition according to claim 9 comprising as a carrier vaseline, lanalcol, cetyl stearate, beeswax.

11. Composition according to any of claims 9 and 10 comprising each active ingredient suspended, emulgated or dissolved in the carrier.

12. Combination and composition according to any of claims 1 to 11 to be used for human and veterinary treatment of the skin epithelial lesions, epithelial deficiency, epithelial injuries of the living skin, external ulcers, burn injuries, necroses caused by irradiation, wounds to prevent or cure infections, to restore the epithelium
    a) said composition comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human and veterinary treatment
        i) a fungicide, which is preferably sparingly water-soluble azole and
        ii) at least one antibacterial compound preferably of the azalide, linkozamide, polypeptide or erythromycin-derivative type and
        iii) a sparingly soluble bacteriostatic sulphonamide,
        iv) an active ingredient promoting circulation of the blood and body fluids preferably azulene or guaiazulene,
        v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide

b) and where said active ingredients are dispersed in a non-aqueous carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 the ratio of the carrier being about 80 - 99 mass% said composition comprising optionally as a further additive a pharmaceutically acceptable colouring agent, a perfume, a volatile oil and said composition being formulated and packaged in the usual manner as an ointment, foam or spray and into the usual dosage forms and units suitable for such administrations and whereby spray formulations may comprise as the carrier a polysiloxane and/or oligosiloxane and optionally a carrier gas to ensure that the composition reaches the surface to be treated.

13. Synergistic composition according to claim 12 *comprising* the following: azithromycin 0,01 - 1,5 mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% preferably in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax.

14. Method of treatment comprising the application of a combination or composition for human and veterinary treatment of the skin bearing epithelial lesions, epithelial deficiency, epithelial injuries of the living skin, external ulcers, burn injuries, necroses caused by irradiation, wounds (in the following "wounds"), to restore the epithelium while preventing or curing infections against such microbes which are pathogenic in humans or animals and which appear together or which represent a danger to appear together **comprising** the local application of a combination containing at least one active ingredient which is effective against several of the fungal and bacterial

strains (opportunally pathogenic on humans and animals) of the group consisting of *fungi* Candida, Aspergillus, and/or Fusarium, and aerobic *bacteria*: Gram-negative bacilli such as Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus, Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species and Mycobacterium species such as Mycobacterium ulcerans, *microbes* similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

15. Method of treatment according to claim 14 ***comprising*** the application of a combination comprising at least one active ingredient which is effective against several of the opportunally pathogenic microbes: Candida tropicalis, Candida parapsilosis, Candida albicans, Torulopsis (Cand.) glabrata, Fusarium oxysporum, Trishosporon beigelii, Aspergillus flavus, Aspergillus fumigatus, Aspergillis terreus, Aspergillus niger, Mucor spp, Rhizopus spp, and/or Penicilium spp.

16. Method of treatment according to claim 14 ***comprising*** the application of a combination comprising at least one active ingredient which is effective against several of the opportunally pathogenic microbes: Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Enterobacter aerogenes, Enterobacter faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Citrobacter spp, Aeromonas spp,: Neisseria meningitidis, Acinetobacter anitratus, Corynebacterium spp, Bacillus sphaericus, Group D Streptococcus, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus faecalis, Streptococcus spp, Bacteroides fragilis, Bac-

teroides ovatus, Bacteroides spp, Fusobacterium mortiferum, Fusobacterium mucleatum, Peptococcus magnus, Peptococcus assaccharoliticus, Peptostreptococcus anaerobius, Peptostreptococcus micros, Clostridium welchii, Clostridium perfingens, Clostridium spp, Propionibacterium acnes, Eubacterium lentum, microbes similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

17. Method according to claim 14 ***comprising*** application of a synergistic combination preferably in one single composition
    a) said combination comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human and veterinary treatment
        i) a fungicide which is preferably an azole and
        ii) at least one antibacterial compound preferably of the azalide, linkozamide, polypeptide type or erythromycin derivative type and
        iii) at least one sparingly water-soluble bacteriostatic sulphonamide,
    b) and where said active ingredients are dispersed in a non-aqueous carrier which is pharmaceutically acceptable on the site of treatment
    c) and where the mass ratio of said active ingredients amounts to i : ii : iii = 0,1 - 10 : 0,1 - 10 : 10 - 200, the ratio of the carrier being about 80 - 99 mass%.

18. Method of treatment according to any of claims 14 to 17 ***comprising*** the application of a combination comprising as the antifungal agent at least one azole of the group miconazole, itraconazole, econazole, ketoconazole and fluconazole.

19. Method of treatment according to any of claims 14 to 18 ***comprising*** the use of a combination containing as an antibiotic at least one of the following: azithromycin, roxythromycin, clarithromycin, clyndamycin,

clyncomycin, thyrotricin, magainin, cecropine.

20. Method of treatment according to any of claims 14 to 19 ***comprising*** the use of a combination comprising as a sulphonamide sulfamethoxazole.

21. Method of treatment according to any of claims 14 to 20 ***comprising*** the use of a synergistic combination comprising as the active ingredients miconazole, azithromycin and sulfamethoxazole in the mass ratio of 0,1 - 1 : 0,1 - 1 : 15 - 35 preferably in the mass ratio 0,1 : 0,1 : 14.

22. Method of treatment according to any of claims 14 to 21 ***comprising*** the application of a combination or composition
    a) containing
        i) a fungicide, which is preferably sparingly water-soluble azole and
        ii) at least one antibacterial compound preferably of the azalide, linkozamide, polypeptide or erythromycin derivative type and
        iii) a sparingly soluble bacteriostatic sulphonamide,
        iv) an active ingredient promoting circulation of the blood and body fluids preferably azulene or guaiazulene,
        v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide
    b) and where said active ingredients are dispersed in a non-aqueous carrier which is pharmaceutically acceptable on the site of treatment
    c) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 the ratio of the carrier being about 80 - 99 mass%.

23. Method of treatment according to claim 14 to 22 ***comprising*** the application of a synergistic combination comprising the following: azithromycin 0,01 - 1,5

mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% optionally in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax.

24. Method of treatment according to claim 23 comprising the use of a composition in the form of an ointment or spray.

25. Method of treatment according to any of claims 14 to 24 in veterinary use.

26. Medical combination preferably in one single composition against microbes which are pathogenic in humans and animals and which appear together or which represent a danger to appear together,
containing active ingredients and carriers acceptable for human and veterinary treatment namely,
a) comprising only such active ingredients or such form of active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are as follows:
   i) at least one fungicide of the azole type and
   ii) at least one antibacterial compound preferably of the azalide, linkozamide, polypeptide type and
   iii) at least one bacteriostatic sulphonamide,
b) and where said active ingredients are dispersed in a water-free carrier which is pharmaceutically acceptable on the site of treatment
c) and where the mass ratio of said active ingredients amounts to i : ii : iii = 0,1 - 10 : 0,1 - 10 : 10 - 200 whereby the ratio of the carrier amounts to about 90 - 99 mass%
for human and veterinary treatment of cavities of the body, the vagina, the rectum or their epithelium, their mucous membranes, to prevent or cure infections

and lesions, to restore the epithelium thereby preventing or curing infections.

27. Composition according to claim 26 comprising an antifungal ingredient which is effective against several human and veterinary pathogen strains of fungi belonging to the group Candida, Aspergillus and/or Fusarium.

28. Composition according to any of claims 26 or 27 comprising an antifungal ingredient which is effective against pathogen strains of the following fungi: Candida tropicalis, Candida parapsilosis, Candida albicans, Torulopsis (Cand.) glabrata, Fusarium oxysporum, Trishosporon beigelii, Aspergillus flavus, Aspergillus fumigatus, Aspergillis terreus, Aspergillus niger, Mucor spp, Rhizopus spp, and/or Penicilium spp.

29. Composition according to any of claims 26 to 28 comprising at least one active ingredient which is effective against several of the opportunally pathogenic microbes: Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Enterobacter aerogenes, Enterobacter faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Citrobacter spp, Aeromonas spp,: Neisseria meningitidis, Acinetobacter anitratus, Corynebacterium spp, Bacillus sphaericus, Group D Streptococcus, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus faecalis, Streptococcus spp, Bacteroides fragilis, Bacteroides ovatus, Bacteroides spp, Fusobacterium mortiferum, Fusobacterium mucleatum, Peptococcus magnus, Peptococcus assaccharoliticus, Peptostreptococcus anaerobius, Peptostreptococcus micros, Clostridium welchii, Clostridium perfingens, Clostridium spp, Propionibacterium acnes, Eubacterium lentum, microbes similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

30. Composition according to any of claims 26 to 29 comprising at least one active ingredient which is effective against several of the opportunally pathogenic

microbes of the renal and the vaginal cavities and those which are the subjects of the field of microbes which are responsible for sexually transmitted diseases in humans and other mammals such as Neisseria gonorrhea, Trepponema pallidum, Haemophylus ducreyi, Chlamydia trachomatis

31. Combination and composition according to any of claims 14 to 30 to be used for human and veterinary treatment of cavities of the body, the vagina, the rectum or their epithelium, mucous membranes, to prevent or cure infections, to restore the epithelium
    a) said composition comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human and veterinary treatment
    b) comprising only such active ingredients or such form of active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are as follows:
        i) at least one fungicide of the azole type and
        ii) at least one antibacterial compound preferably of the azalide, linkozamide and polypeptide type and
        iii) at least one bacteriostatic sulphonamide,
        iv) an active ingredient promoting circulation of the blood and body fluids, such as azulene or guaiazulene,
        v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide
    c) and where said active ingredients are dispersed in a non-aqueous carrier which is pharmaceutically acceptable on the site of treatment
    d) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 the ratio of the carrier being about 90 - 99 mass%.

32. Composition according to any of claims 26 to 31 comprising as the antifungal agent at least one azole of the group miconazole, itraconazole, econazole, ketoconazole, fluconazole.

33. Composition according to any of claims 26 to 32 comprising as as an antibiotic at least one of the following: azithromycin, roxythromycin, clarithromycin, clyndamycin, clyncomycin, thyrotricin, magainin, cecropine.

34. Composition according to any of claims 26 to 33 comprising as a sulphonamide sulfamethoxazole

35. Synergistic composition according to any of claims 26 to 34 comprising as active ingredient miconazole, azithromycin and sulfamethoxazole in the mass ratio of 0,1 - 1 : 0,1 - 1 : 10 - 35, preferably 0,1 : 0,1 : 14.

36. Composition according to any of claims 1 to 7 comprising as a carrier at least one water-immiscible vegetable or mineral oil, fat and/or wax such as vaseline, lanalcol, cetyl stearate, beeswax or adeps solidus 50 and/or a triglyceride.

37. Composition according to any of claims 9 and 10 comprising each active ingredient suspended, emulgated or dissolved in the carrier.

38. Synergistic composition according to any of claims 26 to 37 comprising the following: azithromycin 0,01-1,5 mass% preferably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% optionally in the form of aetheroleum camomillae and/or aetheroleum millefolii.

39. Composition according to any of claims 26 to 38 in the form of a suppository comprising as a carrier adeps

solidus 50 and/or a triglyceride and optionally as a further additive a pharmaceutically acceptable colouring agent, a perfume, a volatile oil.

40. Composition according to any of claims 26 to 39 which is formulated and packaged in the usual manner as an ointment, foam or spray and into the usual dosage forms and units suitable for such administrations and the spray or foam comprising as the carrier a polysiloxane and/or oligosiloxane and optionally a carrier gas to ensure that the composition reaches the surface to be treated.

41. Composition according to any of claims 26 to 40 for the treatment of body cavities formulated and packaged in the usual manner as a tablet, granule, suppository, foam, oily suspension, spray and comprising optionally further correspondent auxiliary materials.

42. Method of treatment of body cavities to prevent or cure infections and lesions in humans or animals against such microbes which are pathogenic in humans or animals and which appear together or which represent a danger to appear together **comprising** the local application of a combination comprising at least one active ingredient which is effective against several of the fungal and bacterial strains (opportunally pathogenic on humans and animals) of the group consisting of *fungi* Candida, Aspergillus, and/or Fusarium, and aerobic *bacteria*: Gram-negative bacilli such as Proteus, Pseudomonas, enterobacter species, Escherichia coli, Klebsiella, Serratia marcescens, Citrobacter, Aeromonas; Gram-negative cocci such as Neisseria, Acinetobacter species; Gram-positive bacilli such as Corynebacterium species, Bacillus sphaericus, Gram-positive cocci such as Streptococcus species; anaerobic bacteria: Gram-negative cocci such as Bacteroides, Fusobacteria; Gram-positive cocci such as Peptococcus, Peptostreptococcus species; Gram-positive bacilli such as Clostridium, Propionibacterium, Eubacterium species and Mycobacterium species

such as Mycobacterium ulcerans, *microbes* similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

43. Method of treatment according to claim 42 ***comprising*** the application of a combination comprising at least one active ingredient which is effective against several of the opportunally pathogenic microbes: Candida tropicalis, Candida parapsilosis, Candida albicans, Torulopsis (Cand.) glabrata, Fusarium oxysporum, Trishosporon beigelii, Aspergillus flavus, Aspergillus fumigatus, Aspergillis terreus, Aspergillus niger, Mucor spp, Rhizopus spp, and/or Penicilium spp and/or .

44. Method of treatment according to claim 42 ***comprising*** the application of a combination comprising at least one active ingredient which is effective against several of the opportunally pathogenic microbes: Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Enterobacter aerogenes, Enterobacter faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Citrobacter spp, Aeromonas spp,: Neisseria meningitidis, Acinetobacter anitratus, Corynebacterium spp, Bacillus sphaericus, Group D Streptococcus, Staphylococcus aureus, Streptococcus pyogenes, Streptococcus faecalis, Streptococcus spp, Bacteroides fragilis, Bacteroides ovatus, Bacteroides spp, Fusobacterium mortiferum, Fusobacterium mucleatum, Peptococcus magnus, Peptococcus assaccharoliticus, Peptostreptococcus anaerobius, Peptostreptococcus micros, Clostridium welchii, Clostridium perfingens, Clostridium spp, Propionibacterium acnes, Eubacterium lentum, microbes similar to bacteria of the Chlamydia species such as Chlamydia trachomatis.

45. Method according to any of claims 42 to 44 comprising application of a synergistic combination preferably in one single composition
    a) said combination containing only such active ingredients or such form of active ingredients

which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are as follows:

i) at least one fungicide of the azole type and
ii) at least one antibacterial compound preferably of the azalide, linkozamide, polypeptide or erythromycin derivative type and
iii) at least one bacteriostatic sulphonamide,

b) and where said active ingredients are dispersed in a water-free carrier which is pharmaceutically acceptable on the site of treatment

c) and where the mass ratio of said active ingredients amounts to i : ii : iii = 0,1 - 10 : 0,1 - 10 : 10 - 200 whereby the ratio of the carrier amounts to about 90 - 99 mass%

d) for human and veterinary treatment of cavities of the body, the vagina, the rectum or their epithelium, mucous membranes, to prevent or cure infections and lesions, to restore the epithelium thereby preventing or curing infections.

46. Method of treatment according to any of claims 42 to 45 ***comprising*** the application of a combination comprising as the antifungal agent at least one azole of the group miconazole, itraconazole, econazole, ketoconazole and fluconazole.

47. Method of treatment according to any of claims 42 to 46 ***comprising*** the use of a combination containing as an antibiotic at least one of the following: azithromycin, roxythromycin, clarithromycin, clyndamycin, clyncomycin, thyrotricin, magainin, cecropine..

48. Method of treatment according to any of claims 42 to 47 ***comprising*** the use of a combination comprising as a sulphonamide sulfamethoxazole.

49. Method of treatment according to any of claims 21 to 27 ***comprising*** the use of a synergistic combination comprising as the active ingredients miconazole, azithromycin and sulfamethoxazole in the mass ratio of

0,1 - 1 : 0,1 - 1 : 15 - 35 preferably in the mass ratio 0,1 : 0,1 : 14.

50. Method of treatment according to any of claims 42 to 49 for human and veterinary treatment of cavities of the body, the vagina, the rectum and their epithelium and mucous membranes to prevent or cure infections and injuries, to restore the epithelium ***comprising*** the local application of a synergistic composition
    a) said composition comprising the following active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are acceptable for human and veterinary treatment
    b) comprising only such active ingredients or such form of active ingredients which are sparingly soluble in water at 20 to 100 °C (<50 µg/ml at room temperature) and which are as follows:
        i) at least one fungicide of the azole type and
        ii) at least one antibacterial compound preferably of the azalide, linkozamide, polypeptide or erythromycin derivative type and
        iii) at least one bacteriostatic sulphonamide,
        iv) an active ingredient promoting circulation of the blood and body fluids, such as azulene or guaiazulene,
        v) an active ingredient promoting epithelization preferably a water-insoluble zinc salt such as zinc oxide
    c) and where said active ingredients are dispersed in a non-aqueous carrier which is pharmaceutically acceptable on the site of treatment
    d) and where the mass ratio of said active ingredients amounts to i : ii : iii : iv : v = 0,1 - 10 : 0,1 - 10 : 10 - 200 : 10 - 100 : 10 - 250 the ratio of the carrier being about 90 - 99 mass%.

51. Method of treatment according to claim 42 to 50 comprising local use of the following combination in the form of a tablet, effervescent tablet, suppository, ointment or foam: azithromycin 0,01 - 1,5 mass% pref-

erably 0,02 mass%, miconazole 0,01 - 1,5 mass% preferably 0,02 mass%, sulfamethoxazole 1 - 19 mass% preferably 2,8 mass%, zinc oxide 3 - 4 mass%, azulene 0,05 - 0,20 mass% preferably 0,12 mass% preferably in the form of aetheroleum camomillae and/or aetheroleum millefolii and as a carrier optionally vaseline, lanalcol, cetyl stearate, paraffin-wax and/or beeswax.

52. Method of treatment according to claim 51 comprising the use of a composition in the form of a suppository comprising as a carrier adeps solidus 50 and/or a triglyceride.

53. Method of treatment according to any of claims 42 to 52 in veterinary use.

STATEMENT UNDER ARTICLE 19(1) (Rule 46.4)

Re: AMENDMENT under Article 19 of
Patent Application N° PCT/HU02/00115 of
HUMAN Rt., Hungary and inventors Lukács K. et al.
Mailed: 06.05.2003 (fax and special delivery)

1. The invention claims new combinations for topical use comprising three "sparingly soluble" active ingredients: a fungicide, an antibacterial agent and a bactericidal sulfonamide. Water solubility is defined: <50µg/ml (room-temperature). Two main fields of use are: skin lesions e.g. burns, ulcers, wounds and treatment of body cavities e.g. vagina, rectum, their mucous membranes etc. Active ingredients are dispersed in a non-aqueous carrier the ratio of which is 80 to 99% for drugs of the skin and 90 to 99,8% for drugs for cavities. Human and veterinary applications are exemplified.

   The biological selection of active ingredients is based on the nature of microbes to be attacked on the target territories.. Water-insolubility the second basis of selection avoiding systhemic resorption and thus high concentration on the spot can be ensured without the danger to expose the patient to systemic antibiotics or fungicides.

   For azithromycine, miconazole and sulfamethoxazole experimental evidence of a well defined synergistic activity is documented in the specification.

2. The search report accepted original claims 12 to 16, 19-20 as novel and inventive and referred to WO 9603135 as novelty destroying of claims covering drugs for cavity-

treatment. WO 9603135 claims vaginal suppositories. Our claims related to skin treatment were found to be novel.

The suppository of WO 9603135 is based on a totally different (unknown) selection of various active ingredients. There was a certain overlapping in certain enlisted active ingredients which has been eliminated by the amendment of our claims. WO 9603135 applies water-soluble active ingredients in a rather high absolute dose (≈1,4g) and relative ratio (≈30%) in polyethylene-glycole which per se is not water-free. The actives include antibiotics e.g. chloramphenicol and erythromycin, antiprotozoal azoles, the water-soluble sulphonamide sulfadimidine, water-soluble fungicides clotrimazole (solubility 0,01 mg/ml), natamycine, nystatine and optionally borax. Only the combination of chloramphenicol, sulfadimidine, clotrimazole and metronidazole (all water-soluble) is exemplified in an extremely high dose (1,47 g per suppository). No biological tests are disclosed.

3. To distinguish over the cited prior art our claims were amended to form two distinct groups: new claims 1 to 15 claim only drugs for skin treatment while claims 26 to 53 claim only drugs for treatment of cavities. Any and all overlapping active ingredient was cancelled from both groups. Drugs for cavities were further limited by narrowing the ratio of the active ingredient. It is emphasized that all active ingredients are sparingly soluble in water - maintaining the original definition of <50µg/ml. It is emphasized that the carrier is non-aqueous. The special combination showing synergism is specially claimed for both groups.

4. It is sincerely believed that - specifically after amendment of the claims - the difference between the prior art disclosure and the present invention is evident and that the claims on file are new over the cited art.